RCMOS - Multidisciplinary Scientific Journal of Knowledge.
ISSN: 2675-9128. Sao Paulo-SP.

Year V, v.1, n.1, Jan/July 2025. | submission: 05/05/2025 | accepted: 07/05/2025 | publication: 09/05/2025

Application of nanotechnology in skin hydration with hyaluronic acid

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SUMMARY

Skin hydration is the system of hygroscopic and lipid agents that together retain water in the skin, and is an extremely important factor when it comes to skin health. A series of factors
are related to the degree of skin hydration such as the production of lamellar lipids, those excreted by the sebaceous gland and the natural hydration factor, these substances balance the speed of transepidermal water loss and the water retention necessary for healthy skin.
One of the components that helps in the production of NMF *(Natural Moisturizing Factor)* is the acid
hyaluronic acid, a glycosaminoglycan, and has the hydroscopic capacity to retain up to 1000 times the
its weight in water, for this reason it has been widely used by the cosmetics industry in order to
enhance the effectiveness of moisturizers. However, it is a molecule that is originally too large to permeate the stratum corneum, and requires modifications or vectorization. Based on these factors,
The present study aimed to present the cutaneous permeation of vectorized and free form hyaluronic acid, through a bibliographic review. It was concluded that the nanoencapsulated active is capable of reaching deeper layers of the skin, thus penetrating the intercellular pathway. It crosses the stratum corneum and reaches the dermis, and with controlled release, it promotes a longer time of action of the active, maintaining the water content for a longer period than the active in free form.
Keywords: Skin Hydration; Hyaluronic Acid; Nanotechnology

ABSTRACT

Skin hydration is the system of hygroscopic and lipid agents that together retain water in the skin and is
an extremely important factor when it comes to its health. A series of factors are related to the degree of skin hydration, such as the production of lamellar lipids, those secreted by the sebaceous gland, and the natural moisturizing factor, these substances balance the speed of transepidermal water loss and the water retention necessary for healthy skin. One of the auxiliary components in the production of NMF (Natural Moisturizing Factor) is hyaluronic acid, a glycosaminoglycan, and has a
hydroscopic capacity to retain up to 1000 times its weight in water, which is why it has been widely
used by the cosmetics industry to enhance the effectiveness of moisturizers. However, it is a molecule

that is originally too large to permeate the stratum corneum, requiring modifications or vectorization. Based on these factors, the present study aimed to compare the effectiveness of vectorized and free form hyaluronic acid, through a bibliographic review. It was concluded that the nanoencapsulated active is capable of reaching deeper layers of the skin, thus penetrating the intercellular pathway. It crosses the stratum corneum and reaches the dermis, and with controlled realese, it promotes a longer action time of the active, maintaining the water content for a longer period than the active in free form.

Keywords: *Skin Hydration; Hyaluronic Acid; Nanotechnology*

1. INTRODUCTION

The present article aimed to present the permeation of vectorized hyaluronic acid and in free form and their differences. Initially, the anatomical and physiological constitution of the skin, divided into 3 layers: epidermis, dermis and hypodermis.

The stratum corneum is the most superficial layer of the epidermis and acts as a barrier. formed by keratinized cells, called corneocytes, which act as bricks, connected by corneodesmosomes, enclosed in a lipid matrix that resembles cement. This model received the name *brick* and *mortar* format , where the corneocytes and lipid matrix prevent loss of transepidermal water. (HARRIS, 2016)

The skin has natural moisturizing factors such as amino acids, urea, lactic acid and hyaluronic acid that supports water retention. Despite the skin's natural protection, it can suffer external and internal interferences such as the products used and water intake. Observing these points, the cosmetic industry proposes cosmetic hydration and it can be done in 3 ways: occlusion, emollience and moisturization. The present study focused on the latter route, that of moisturization, since the acid Hyaluronic acid acts in this way on the skin, being an active ingredient that can retain up to a thousand times its weight in water, being one of the best moisturizing actives, making it relevant as an object of study, acting in maintaining the skin barrier, maintaining healthy and functional epithelial tissue. However, there is two types of hyaluronic acid, the high molecular weight one remains superficially in the skin, not allowing transepidermal water loss; and low molecular weight, can enter the deeper layers of the skin, having a greater effect. (VALACHOVÁ *et* al., 2022; AMARAL, 2009)

In addition to this factor that modifies the hydration level, there is also hyaluronic acid. vectorized, the focus of this study, which performs a gradual delivery of the active ingredient, unlike acid hyaluronic acid in free form. Providing immediate but shorter-lasting hydration, the acid Vectorized hyaluronic acid releases it according to the tissue's needs, according to the gradient concentration, pH, temperature can expand or contract the matrix to release the active, keeping it hydration of the tissue for a longer period of time, a very important factor given that hyaluronic acid in

free form lasts less than 1 day in the tissue. (TOKUDOME *et al.,* 2018; BIZERRA, 2016)

This fact occurs because nanomaterials have special nanophysical and chemical characteristics. due to its size and the freedom to change its properties, helping to direct the drug or active for the specific tissue, increasing bioavailability and efficacy, in addition to increasing the half-asset life. (MATALQAH *et al.,* 2024)

Nanoencapsulated actives facilitate penetration by reducing hydrophilicity, when use hydrophobic materials as a vector, protect the active ingredient from degradation by hyaluronidase or free radicals, and has the ability to perform a progressive, longer-lasting and targeted release, prolonging hydration (MATOS *et al.,* 2018).

Therefore, the research will provide more information about the performance of hyaluronic acid in skin hydration when nanoencapsulated.

2 THEORETICAL FRAMEWORK

2.1 Anatomy and physiology of the skin

The skin or epithelial tissue is the tissue that covers the body, with a complex structure and numerous functions. According to MCKNIGHT *et al.* (2022) the skin is responsible for controlling the body temperature, metabolize vitamin D, absorption and secretion of liquids, protection against external agents, absorption of ultraviolet light, waterproof barrier, in addition to aesthetic and sensory, maintaining the integrity of the organism, ensuring homeostasis.

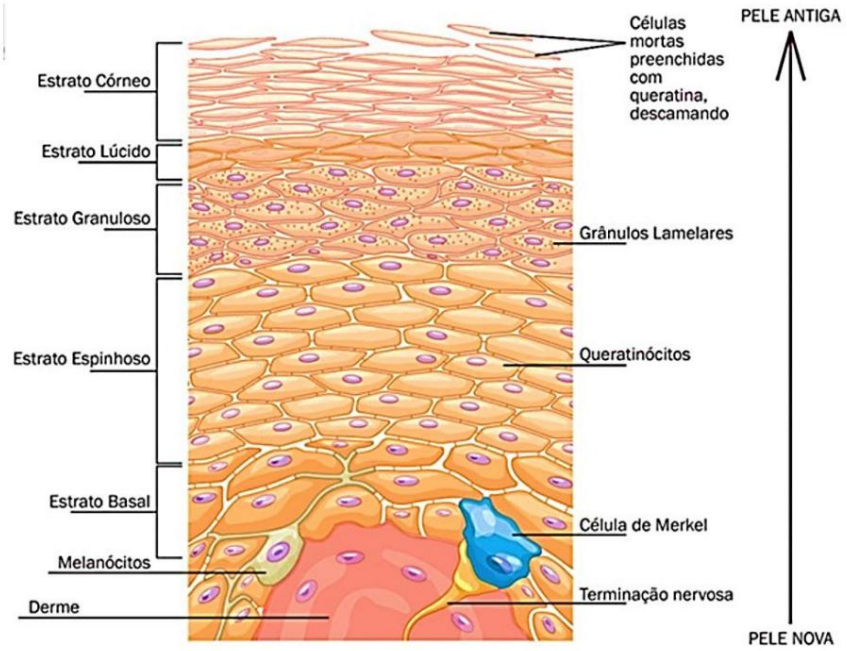
> The skin is divided into three main regions: the epidermis (outermost epithelial tissue: from the Greek epi = on, derma = skin), the dermis (connective tissue to which the epidermis attaches through of the basement membrane) and the hypodermis, the deepest layer characterized by the presence of fat (hypo = lower, derma = skin). (HARRIS, 2016, p. 16)

2.1.1 Epidermis

The epidermis is the outermost layer, consisting of stratified squamous epithelium. keratinized, formed mostly by keratinocytes (keratin producers), in addition to Langerhans cells (defense cells), Merkel cells (dendritic cells that confer sensitivity) and melanocytes (dendritic cells that produce melanin). It is further divided into sublayers: basal, spinous, granular, lucid and horny. The basal or germinal layer has high levels of mitosis, causing the tissue to renew itself every 15 to 30 days (JUNQUEIRA; CARNEIRO, 2017). In Figure 1 you can

the distribution of the layers of the epidermis must be observed.

Figure 1 – Distribution of epidermal layers



Source: Federal University of Alfenas [sd]

The granular layer presents cells surrounded by lipid bilayers, one of the factors to form the skin barrier (BLEACH *et al.,* 2017; ZHOU *et al.,* 2019).

The cells of the stratum granulosum are surrounded by lipid bilayers because in the stratum below: spiny, have lamellar granules, responsible for the beginning of keratinization, migrating to the granular layer expelling lipids such as ceramides, fatty acids and cholesterol, and enzymes (proteases, acid phosphatase, lipases and glycosidases). In addition, it is bound by desmosomes, for this This reason is called the spinous layer (BAUMANN, 2004).

“The epidermal factory”: progressive layers and corresponding production steps can be observed in Figure 2.

Figure 2 - “The epidermal factory”: progressive layers and corresponding production steps

Source: Rosso; Levin (2011)

The pilosebaceous follicle (hair follicle + sebaceous gland) is present in invaginations of the epidermis. The sebaceous glands produce sebum (controlled by hormonal action) and it reaches the layer cornea through the follicular canal, and flows into the ostium, transferring proteins to the stratum corneum, lipids and glycerol aiding in hydration. (FERNANDES, 2016)

2.1.2 Dermis

The dermis is found below the epidermis, with vascularization, formed by connective tissue, providing support to the adjacent layer, with collagen, elastic and reticular fibers, proteoglycans and glycosaminoglycans (GAGs). (DAMAZIO; GOMES, 2017; BRAVO *et al.,* 2022)

GAGs are responsible for the formation of the extracellular matrix, and their composition is linear polysaccharides, such as: chondroitin sulfate, dermatan sulfate, keratan sulfate, heparan sulfate, heparin and hyaluronic acid. This is the only one that is not sulfated, and can be present in different forms depending on the pH, salt concentration, among others. (BRAVO *et al.,* 2022)

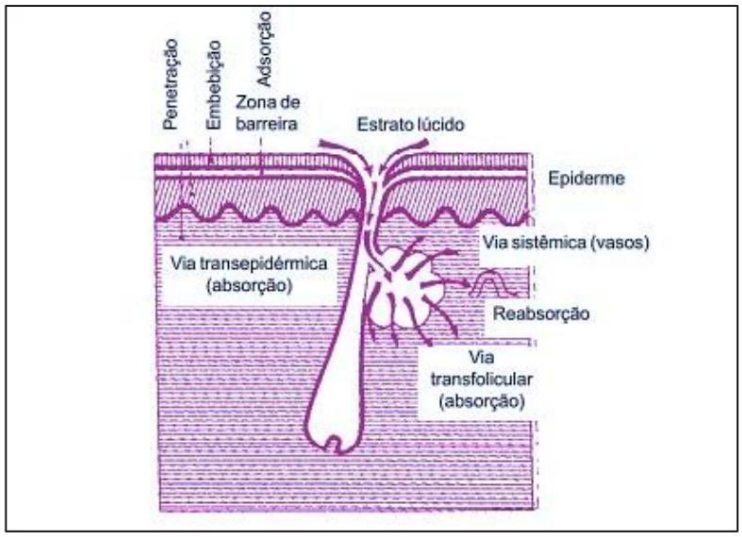
The main molecules of the extracellular matrix are GAGS, proteoglycans, growth factors growth and structural proteins such as collagen, but the predominant one is hyaluronic acid, It can be said that 50% of the hyaluronic acid in the human body is found in epithelial tissue. (PAPAKONSTANTINOU, 2012)

2.2 Skin permeation pathways and nanotechnology

According to (BENY, 2016), the skin barrier is made up of three structures: hydrolipidic mantle (emulsion of water and natural moisturizing factors) and lipids from the sebaceous gland; stratum corneum where keratinization of corneocytes occurs, making them impermeable to water, in addition to presence of lipids preventing skin dehydration; granular layer where kerato-granules hyaline are accumulated by keratinocytes during the process of epidermal differentiation.

The skin constitutes an effective and selective barrier to chemical permeation, with the stratum corneum the main controller. In addition, the cosmetic formulation in free form encounters sebum, microorganisms and cell debris that hinder permeation. Thus, there are 3 permeation pathways: Intercellular (between corneocytes), transfollicular (through hair follicles), or through glands sweat glands. (BARRY, 2001). Skin permeability is shown in Figure 3.

Figure 3 - Skin permeability



Source: Beny (2013)

Many factors influence the penetration of active ingredients: such as their molecular weight, the system used to deliver them, such as denaturation of the hydrolipidic mantle, concentration of substances. But also in relation to the skin: integrity of the stratum corneum and hydration (LANE, 2013; ALKILANI *et al.,* 2015; SILVA *et al.,* 2020 *apud* FRANCO 2020).

In order to facilitate permeation, some chemical promoters are used, increasing the

hydration, facilitating the transdermal route, which may favor the extraction of lipids or proteins, disorganization of the lipid layer, the formation of lipophilic complexes, among others. Despite aid in permeation, chemical promoters can irritate the skin if they interact with keratinocytes, leading to dermatitis, inflammation, erythema, among others (SILVA; APOLINÁRIO, 2010; KARANDE *et al.,* 2005).

The skin has natural protection against compounds foreign to its system (xenobiotics), making it difficult for drugs to permeate, in these cases nanotechnology is a great ally, as overcomes these obstacles, taking the active ingredients to the pilosebaceous units and improving their retention. nanoparticles on the target, releasing a portion with localized effect, creating reservoirs at the site (FERNANDES, 2016)

2.3 Physiological and Cosmetic Skin Hydration

Skin hydration is possible due to the skin's protective barrier against water loss transepidermal, built on the bricks and mortar model, where the lipids are distributed in

40% ceramides, 20% cholesterol and 25% fatty acids, after being expelled by the lamellar granules. In addition, lipids are also secreted by the sebaceous gland. These lipids coming from different pathways, together with the NMF - natural moisturizing factor, carry out the control water. Before being expelled by the lamellar granules, lipids are produced inside the epidermal keratinocytes, and only then are they distributed throughout the lamellar bodies in the stratum granulosum, organized into lipid bilayers. These are the effective hydration barrier of the stratum corneum by regulate water content. The alternating layers have hydrophilic “heads” and “tails” hydrophobic (BAUMANN, 2004; DRAELOS, 2016)

> The natural moisturizing factor – NMF, refers to amino acids that have the capacity hygroscopic. Together, they have the function of maintaining the hydration and microbiota of the skin, in addition to the average pH between 5.4-5.9 in most parts of the body. (SOUZA *et* al., 2020, p.7)

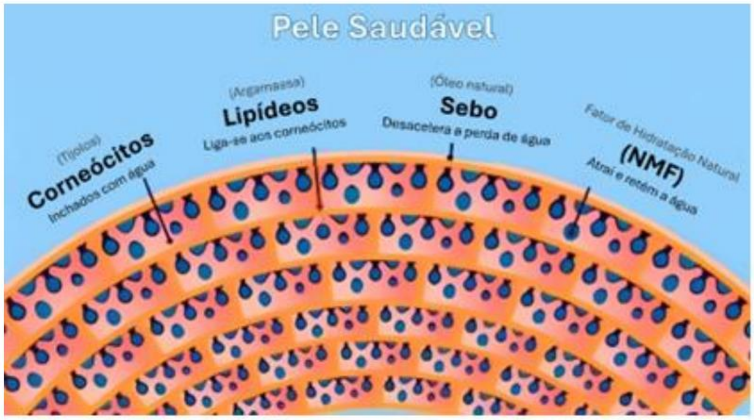
NMF is formed through the degradation of filaggrin (a protein that aggregates filaments of keratin to form the extracellular matrix of the stratum corneum). It is degraded into amino acids and metabolites and are present within the cells of the stratum corneum, making them humectants. (LESLIE, 2004)

As water levels decrease in the epidermis, filaggrin is broken down into amino acids, to attract and retain water, maintaining water control. If the water content becomes low, the corneocytes are unable to detach, leading to rough skin, as activities

enzymatic activities are impaired. (DRAELOS, 2016)

These components of the stratum corneum linked to skin hydration can be observed in Figure 4, below:

Figure 4 - Components of the stratum corneum



Source: ESTELRICH (2024)

In this way, moisturizing cosmetics aim to assist the physiological processes mentioned above. maintenance of the epidermal barrier, aiming to improve water levels in the tissue, preserving the homeostasis through 3 main pathways: Emollience: forms a film over the skin, preventing water loss transepidermal when incorporated into lipids, in addition to providing softness. Wetting: Forms a film on the skin, which is responsible for attracting water molecules from the dermis to the surface of the stratum corneum, and regulate the number of filaggrins. Occlusive: Reduce transepidermal water loss by forming a hydrophobic film on the surface of the fabric, antimicrobial peptides increase and aid in the differentiation of keratinocytes. It is common for an occlusive agent to act as emollient at the same time. In short, a good moisturizer should contain occlusives, emollients and humectants. (MATOS, 2016; RIJKUMAR *et* al., 2023)

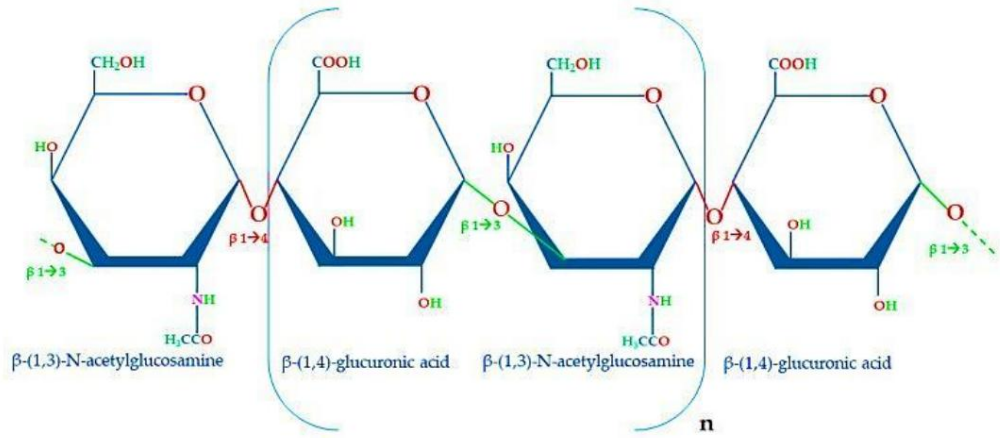
2.4 Hyaluronic acid

Hyaluronic acid (HA) is a glycosaminoglycan compound, consisting of glucuronic acid and N-acetylglucosamine, linked by glycosidic structures, with macromolecular structure and high polymerization, being the only non-sulfated glycosaminoglycan. Unlike the others glycosaminoglycans, is synthesized on the cytoplasmic surface of the plasma membrane of fibroblasts by enzymes called hyaluronan synthase, instead of the golgi apparatus. (LACONISI *et*

al., 2023)

According to Leslie (2004) “They are made up of polysaccharide chains composed of units repeated chains of disaccharides that are attached to a protein core”, as seen in Figure 5:

Figure 5 - Chemical Structure of Hyaluronic Acid



Source: Laconisi *et al,* (2023)

Molecular weight is defined according to the number of repeating acid units glucuronic and N-acetylglucosamine. 6- 200 Kda (low molecular weight); 0.2- 1.0 Mda (medium molecular weight); molecular); > 1 Mda (high molecular weight). (LACONISI *et al.,* 2023)

It helps with skin hydration, support and elasticity by maintaining collagen fibers. whole. In humans, half of it is found between the dermis and epidermis, and in the body as a whole, there are 15 g of hyaluronic acid for every 70 kg. It is produced mainly in fibroblasts in the dermis, but with the aging process, this production decreases, which causes the epidermis has lower water retention. (MORAES *et al.,* 2017; BARRICHELO *et al.,* 2020; SHANG *et al.,* 2024)

Hyaluronic acid can be metabolized by 3 proteins that produce different weights molecular. The HAS1 and HAS2 proteins have a lower production, and offer as a product the high molecular weight hyaluronic acid, while HAS3 provides low molecular weight hyaluronic acid molecular. This is used on the skin for a maximum of one day and can be degraded by hyaluronidases (enzymes) and non-enzymatic agents such as free radicals or chemical reactions such as acid hydrolysis or alkaline. (BRAVO *et al.,* 2022)

The molecular weight of hyaluronic acid directly influences the actions of this substance with tissues. High molecular weight hyaluronic acid (above 1000 kDa) is antiangiogenic and

immunosuppressant, while low molecular weight ones induce angiogenesis and inflammation. Due to these factors, when the tissue is ruptured, the synthesis of hyaluronic acid is increased so that it occurs tissue repair. (SMEJKALOVA *et al.,* 2015; SNETKOV *et al.,* 2020; PAPAKONSTANTINOU, 2012)

For both cosmetic and other uses, hyaluronic acid can be obtained in two ways: forms: animal tissues or microorganisms. When obtained from animal tissues, hyaluronic acid can be degraded by hyaluronidase present in animal tissue, losing part of the content and may also contain impurities, which can cause complications, as well as chances of allergies. Another The way to obtain it is through bacteria that produce HA as a secondary metabolite, however release bacterial endotoxins, which is why they started using genetically modified strains modified. (LACONISI *et al.,* 2022)

2.5 Hyaluronic Acid and Skin Hydration

Topical use of hyaluronic acid is highly recommended, as it is a non-toxic substance. immunogenic, non-toxic and non-inflammatory, and compatible with the skin (SHANG *et al.,* 2024).

Its water retention capacity is due to the density of negative charges in the groups carboxyl in its structure, which generates osmotic pressure, attracting water molecules, being able to retain up to 1000 times its weight in water, making it highly hydrophilic. Approximately 6 liters of water in just 1g (VALACHOVÁ *et al.,* 2022; JEGASOTHY *et al.,* 2014).

In cosmetics, molecular weight is used in the following characteristics (MATALQAH, *et al.,* 2024) as presented in the Table.

Table 1- Molecular weight of hyaluronic acid and its characteristics

Molecular Weight	**Kda (value range)**	**Features**
Low	5-20	ability to penetrate better into the tissue, hydrating and aiding in collagen synthesis
Average	20-200	balances water retention and penetration
High	>200	forms a film on the skin, preventing water loss transepidermal

(Source: Author)

Figure 6 - Permeation of hyaluronic acid with various molecular weights

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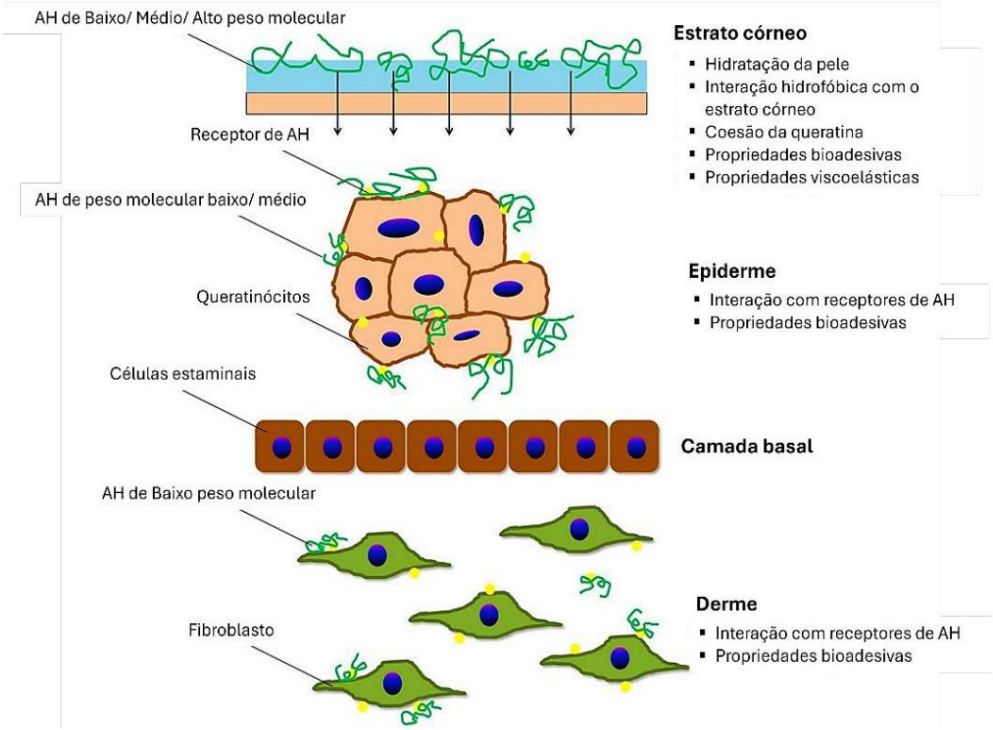
ISSN: 2675-9128. Sao Paulo-SP.



Source: Bravo et *al.,* (2022)

Hyaluronic acid remains in the body for a short period of time, until it is degraded by hyaluronidases, or by free radicals, remaining in the skin for less than a day. For this reason, when added to a cosmetic formulation, it must be protected from chemical modifications as bonds to decrease hydrophilicity, being mixed with hydrophobic materials, forming insoluble or hydrogel derivatives (SMEJKALOVA *et al.,* 2015; PAPAKONSTANTINOU, 2012)

2.6 Cosmetic Nanotechnology

> The concept of nanotechnology is to study objects on a nanometric scale. Products are created with special physical and chemical properties through atomic-scale materials and molecular. Nanometric systems include substances of 1 and 100 nm or up to 999 nm (microparticles), varying according to the school of thought (FERNANDES, 2016, p.26)

The advantages of nanocarriers are: intensifying penetration in speed and portion of the drug; deliver the molecule to the target without affecting other organs and tissues; entrapment effectiveness, maintaining physical and chemical properties; accommodating both lipophilic and hydrophilic drugs; increase the time of action of the drug; minimize toxic effects; protection against hydrolysis and

oxidation. (GARG, 2014)

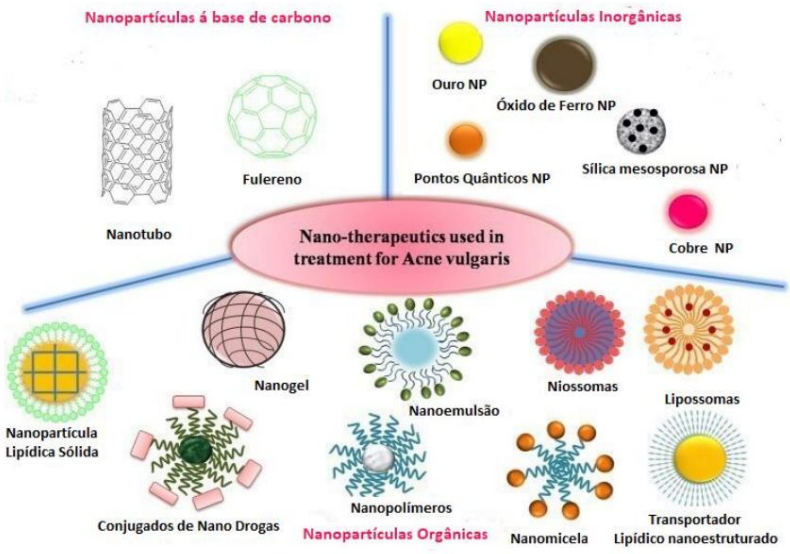
In conventional administration therapies, a drug peak is common, which then decays, requiring a new dosage. Thus, nanostructured systems can modulate the release and maintain the therapeutic range for longer. (BIZERRA; SILVA, 2016)

The interaction of nanoparticles with the skin depends on their size and charge, their ability to loading of the medication and the means of administration. (CHAKRABORTY *et al.,* 2022)

Increased effectiveness due to three factors: delivering the active ingredient to deeper layers of the epidermis, increased tissue hydration and stabilization of the active ingredient, also of the labile ingredients, release gradual asset allocation. (SOUZA; ANTUNES, 2020)

The active release mechanisms are usually of 3 types: drug desorption adsorbed to the surface, diffusion of the carrier matrix, erosion of the carrier matrix or process combined erosion and diffusion. There are now new transport models in nanotechnology cosmetics such as niosomes, liposomes, emulsomes, transferosomes, microemulsion, nanoemulsion, and nanolipid carriers (GARG *et al.,* 2013). As can be seen in the figure 7 and in table 1, below:

Figure 7 - Schematic representation of several nanoparticles applied in Acne vulgaris treatment



Source: CHAKRABORTY, *et al.,* (2022)

Table 1 – Types of nanoparticles

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ISSN: 2675-9128. Sao Paulo-SP.

Nanoparticles Composition		Main	How they work	Authors
Systems Inorganic	Solid structure, which supports two or more components.	Gold, silver, titanium, ...	They are antioxidants and antimicrobials.	CHAKRABORTY, *et al.* (2022)
Systems Polymeric	Colloidal structures, usually encapsulated by polylactic acid or polylactic-glycolic acid.	Nanocapsules (vesicular structure) or nanospheres (matrix structure)	Perfect for delivering encapsulated lipophilic actives to the skin.	MORAIS (2018)
Systems Lipids	Lipid systems are structures with large amount of sebum inside, generally produced by cetyl phosphatidylcholine palmitate. and	Liposomes, nanoemulsions, SLN (solid lipid nanoparticles) and NLC (nanostructured lipid carriers)	It permeates better due to its similarity to the epidermis. They can encapsulate lipophilic and hydrophilic substances.	MATOS *et al.* (2018)

(Source: Author)

When nanoparticles are applied to the stratum corneum, the water evaporates and the particles form an occlusive film on the skin, improving hydration and the passage of active ingredients. They also diffuse into the follicles (transfollicular route) and can also reach the systemic circulation. (FERNANDES, 2016)

Nanomaterials are represented by lipids, polymer-based nanosystems, NPs (Polymeric Nanoparticles) metal-based additional nanosystems. (MORAIS, 2018)

2.7 Nanoencapsulated hyaluronic acid

Hyaluronic acid molecules are 3,000 nm in diameter, the space between corneocytes is from 15 to 60 nm and the hyaline membrane from 6 to 10 nm, which makes it difficult to penetrate the dermis. Then scientists at Forlle ÿd Laboratories in Japan managed to reduce hyaluronic acid through

hydrolysis to the nano (5nm) without altering the structure, taking the active ingredient to the dermal level (JEGASOTHY *et al.,* 2014)

Thus, a solid-in-oil (S/O) technology was created, where water-soluble substances are nanocoated on oily materials for penetration of high molecular weight substances, however These assets can be inactivated by going through the freeze-drying process. (SHIGEFUJI; TOKUDOME, 2020)

One of the most widely used hyaluronic acid encapsulation systems is the liposome. its ability to encapsulate hydrophilic actives such as hyaluronic acid and have high biocompatibility by fusing with the skin, thus increasing the half-life of proteins, peptides and drugs in general. (MATOS, *et al.,* 2018)

3. MATERIAL AND METHOD

The study had a qualitative-quantitative exploratory nature in order to report the effectiveness of nanotechnology in skin hydration with the use of hyaluronic acid. For the development of theme a bibliographic survey was carried out, using the databases of *PubMed, Scielo,* Google Scholar and books, during the period from February 2024 to February 2025.

In order to delimit the theme, the keywords “cosmetic nanotechnology, nanotechnology, skin hydration, hyaluronic acid” and in English *“cosmetic nanotechnology, nanotechnology, skin hydration, hyaluronic acid”* being compiled publications in Portuguese and English.

3. RESULTS AND DISCUSSION

As demonstrated throughout this literature review, the challenges of using acid hyaluronic acid in skin hydration are: skin permeation and stability of the active ingredient. In this way, nanotechnology is used to overcome such adversities.

Many studies have been carried out to prove the efficiency of formulations using hyaluronic acid and nanotechnology. The main research will be discussed below and also presented, in summary form, in Table 2.

Table 2 – *In vivo* and *in vitro* research on the use of vectorized and non-vectorized hyaluronic acid

Search	Quite	Results	Authors
Acid research hyaluronic encapsulated in polyion complexes	mouse skin excised	Hyaluronic acid remained in skin surface, while vectorized hyaluronic acid Performed in was observed in the lipid intercellular, concluding that hyaluronic acid penetrates transcellularly, while vectorized hyaluronic acid intercellularly since the vehicle is broken down in the tissue by ions in the stratum corneum or in deeper layers.	SHIGEFUJI; TOKUDOME (2020)
Search with liposomes encapsulating hyaluronic acid	Held on cellulose and in human skin	Liposomes deposited in the stratum corneum are adsorbed and remain intact on the surface or become flattened and transform into bilayers multilayered planar lipids. or At this moment the active ingredient is released due to the interaction of the phospholipids of the liposomes with you and phospholipids of the stratum corneum. Thus, hyaluronic acid crosses the stratum corneum.	GONZALEZ *et al.* (2015)
Hyaluronic acid in pollions	Excised mouse skin in vitro	acid hyaluronic nanoencapsulated was able to reach the dermis, while free hyaluronic acid did not permeate beyond the stratum corneum. As for water loss transepidermal, it was observed that it was lower in the group in which nanoencapsulated hyaluronic acid was used than in the free form.	TOKUDOME et al. (2018)

Shigefuji, Tokudome (2020), evaluated the penetration of HANP (acid nanoparticle

hyaluronic acid) of poly-l-lysine compared to the penetration of high-weight hyaluronic acid (HA) molecular. For this, skins of hairless male mice were used, excised from total thickness. As a result, the authors present the adsorption rates of HA and HANP at keratin and also the adsorption rates to a complex of liposomal stratum corneum lipids (SCLL) that mimic the composition of skin lipids (in vitro model). Thus, it was seen for keratin adsorption values of 11.8 for AH and 5.5% for HANP, while adsorption in SCLLs was 1.2% for HA and 8.2% for HANP, in other words, HA has an occlusive action on skin surface while HANP is able to penetrate the intercellular spaces. Furthermore, it was It was also observed that HANP with poly-l-lysine showed low degradation of these lipids intercellular.

Additionally, it is worth noting that HANP decomposes after penetrating the skin and then functions as HA in the skin. However, it is unclear whether HANP is destroyed on the skin surface when it comes into contact with the stratum corneum or if it decomposes in the skin after penetrating the stratum corneum. The ions are believed to have a significant effect on HANP degradation. It has been reported that the concentration of calcium ions in the stratum corneum is low and the concentration of calcium ions increases towards the dermis. Thus, it is hypothesized that HANP does not disintegrate soon after application to the skin and yes that disintegration occurs slowly after penetrating the skin; however, this requires further investigation.

González *et al.* (2015), in turn, investigated the release and permeation of hyaluronic acid (AH) liposomed in an ex vivo model of human skin (including the stratum corneum) obtained from abdomens of healthy women. The liposomes evaluated were evaluated in 3 types of formulations: HA-loaded liposomes (F1), HA-loaded liposomes + 0.15% Tween® 80 (F2) and HA-loaded liposomes + 3.5% Transcutol® P (F3).

As a result, González *et al.* (2015) observed that the formulation with Transcutol® P (F3) presented the highest cumulative release of HA and the highest release constant, reaching a release of approximately 50% after approximately 30 minutes and a total of just over 65% at the end of 5 hours, followed by the formulation with Tween® 80 (F2), with release around 15% after 30 minutes and approximately 25% after 5 hours and finally the liposomes with AH (F1) with a slower release starting at 5% after 30 minutes and approaching 10% at the end of 5 hours, thus demonstrating a limited release.

In summary, penetration enhancers (Tween® 80 and Transcutol® P) increase both the rate at which they prolong the permeation time of HA from the liposomes through the

skin membranes, with emphasis on Transcutol® P.

It is believed that liposomes are first adsorbed, remaining intact in the surface or flatten out and result in planar or multilayer lipid bilayers as they accumulate and due to this adsorption of liposomes in the skin there is a driving force that induces all the handover process to underlying layers.

The authors also compare the release of HA in a cellulose model and speculate that as F1 showed a slightly higher release in human skin than in cellulose, it is possible that the interaction of liposome phospholipids with stratum corneum phospholipids may be involved in the destabilization mechanism, as is also highlighted by Shigefuji and Tokudome (2020).

Tokudome *et al.* (2018), investigated the delivery of HA nanoparticles formed with protamine polymer in excised skins of hairless male mice and also in skins of mice irradiated continuously for 4 days with ultraviolet B (in vivo) and their water loss transepidermal (TEWL) after these 4 days. It is worth noting that the excised skins had the tissue subcutaneous tissue removed, in addition, two types of excised skin were used in the study: one with the stratum corneum (full thickness) and another with the stratum corneum removed (peeled skin).

In ex vivo findings, HA and aqueous HANP did not penetrate full-thickness skin, while in the desquamated skin the HA remained close to the external surface and the HANP penetrated more deeply. In parallel, AH and HANP were formulated emulsified in diisopropyl adipate or squalane and Pemulen TR-2®. Formulations containing squalane did not result in any full-thickness skin penetration, whether of HA or HANP. On the other hand, the HANP formulation containing diisopropyl adipate in full thickness skin, showed deeper permeation into the skin.

Regarding TEWL, the irradiated groups showed increased rates, however the group HANP showed lower rates when compared to the HA group (+/- 11g/m²/h and +/- 15.5g/m²/h, respectively).

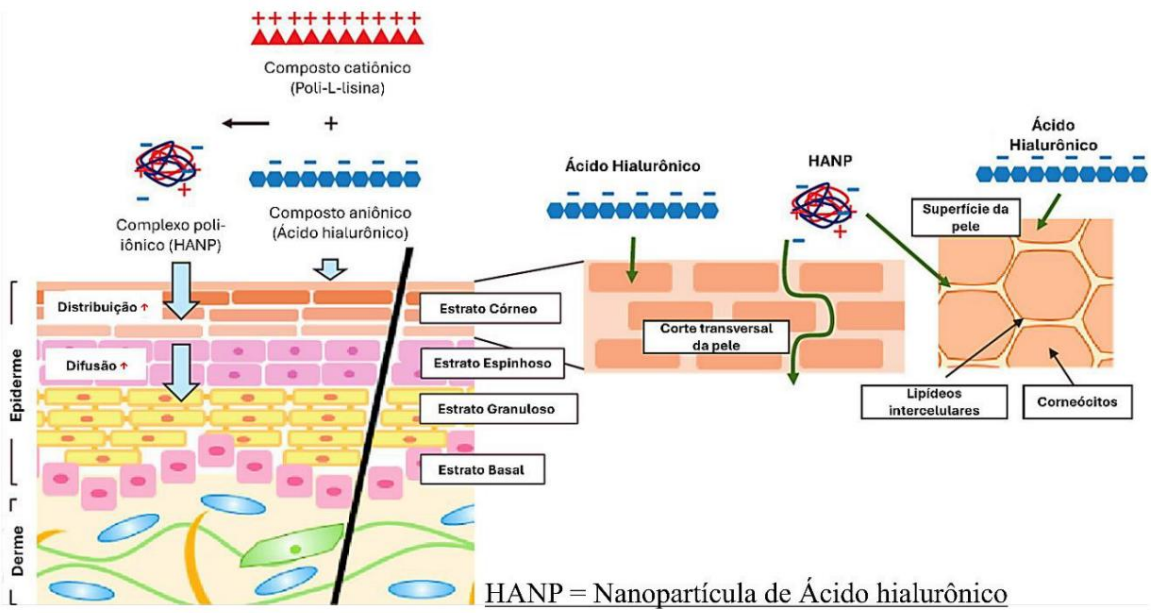
Tokudome *et al.* (2018) concluded that HANP was delivered to the dermis in both exome analysis both in vivo and in vivo, while free HA remained in the stratum corneum. However, it is important highlight that after the application of HANP, HA was found in free form within the skin and not more in nanoparticulate form. As for TEWL caused by UVB irradiation, HANP demonstrated positive results in reducing this rate, showing signs of helping in the recovery of skin barrier.

It is possible to note that Tokudome *et al.* (2018) sought to evaluate a type of polymer (protamine)

different when compared to Tokudome *et al.* (2020) (poly-l-lysine polymer), but still, both showed positive results in increasing permeability. Both results converge with González *et al.* (2015), however the latter had in its method a research experimental on excised skin from women, while Tokudome *et al.* (2018) and Tokudome *et al.* (2020) worked with *ex* vivo and *in* vivo sampling of mice. In addition, González *et al.* (2015) worked with HA nanoparticles, HA nanoparticles + 0.15% Tween 80® and HA nanoparticles + 3.5% Transcutol®, demonstrating a lower penetration potential and permeation time for the group of HA nanoparticles.

In summary, it is observed that nanoencapsulated hyaluronic acid has the ability to penetrate in deeper layers of the skin, reaching the dermis, acting not only as an occlusive on the surface of the skin, but as a humectant in deeper layers, even improving transepidermal water loss, as can be seen in figure 8 below:

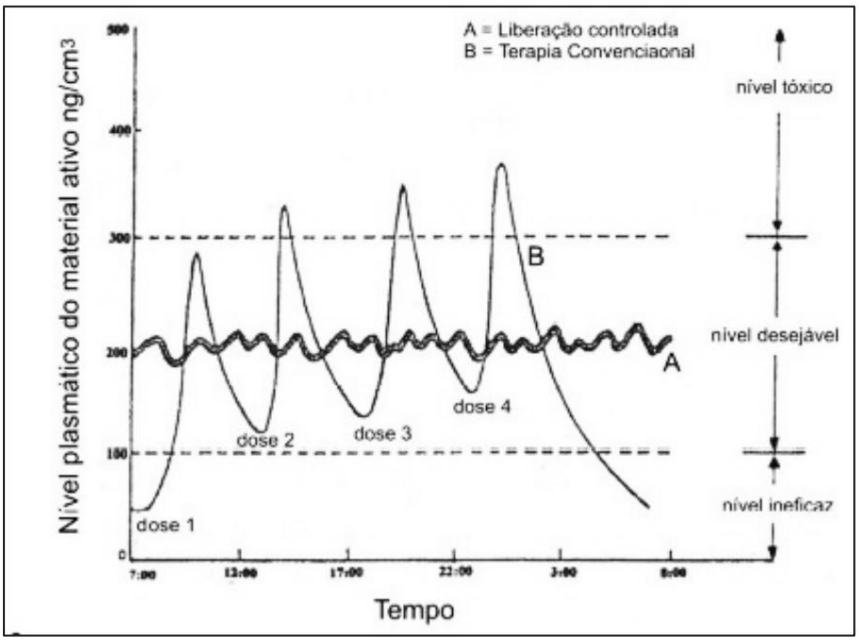
Figure 8 - Penetration of encapsulated and non-encapsulated hyaluronic acid into the skin



Source: Shigefuji; Tokudome (2020)

In addition to the factors mentioned, it is possible to note that in conventional administration therapies it is common that there is a peak of the drug, then it decays, requiring a new dosage. Thus, certain systems nanostructured materials can modulate release and maintain the therapeutic range for longer. (BIZERRA; SILVA, 2016) as can be seen in figure 9.

Figure 9 - Plasma level of active material



Source: Graham, 1978

FINAL CONSIDERATIONS

In summary, the application of nanotechnology in skin hydration with hyaluronic acid is a way to enhance the useful life of this asset, enhancing hydration and reducing need for frequent reapplications. When nanoencapsulated, it can overcome the difficulties permeation originating from its molecular weight and hydrophilicity, and be protected from degradation of hyaluronidases and free radicals, reaching greater depth in the skin, through a release gradual, its effectiveness being influenced by other agents added to the formula. Therefore, it is suggested that if new research is conducted in order to ratify the forms of penetration and permeation as well as evaluate its effectiveness in different nanostructures and formulas.

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ACKNOWLEDGMENTS

I thank God first, who showed me my vocation, and has sustained me in carrying out this work.

To my parents and my fiancé, for understanding my absence, and for calming me down every time I thought I couldn't do it, being a refuge and safe haven, as well as helping me keep me awake in the early hours of the morning when I was tired.

And I couldn't forget to thank the teaching staff who accompany me, taking all the doubts and suggestions for improvement, to professors Isabella Tereza, Márcia Gorny and Felipe Scholz, thank you very much.