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EMERGING NANO-COSMECEUTICALS FOR SKIN REJUVENATION: INTEGRATED APPROACHES WITH NANO-RETINOL, NANO-PEPTIDES, AND SMART DELIVERY SYSTEMS

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Abstract:

Skin aging is a complex biological process driven by intrinsic factors, including genetic and hormonal changes, and extrinsic factors such as ultraviolet (UV) radiation, environmental pollution, and lifestyle-related stressors. These factors contribute to the degradation of structural proteins, particularly collagen and elastin, resulting in wrinkles, loss of elasticity, dryness, and uneven skin tone. Cosmeceutical actives such as retinol and peptides are widely investigated for their ability to enhance cellular turnover, stimulate collagen synthesis, and improve skin appearance. However, their clinical and cosmetic effectiveness can be limited by poor stability, low bioavailability, rapid degradation, and skin irritation. Nanotechnology-based delivery systems have therefore emerged as promising platforms for improving the performance and tolerability of anti-aging cosmeceuticals. This review critically examines the integration of nano-retinol and nano-peptide systems into advanced topical formulations, focusing on their physicochemical characteristics, skin targeting, therapeutic potential, and formulation considerations. Encapsulation of retinol in liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) can improve photostability, controlled release, skin deposition, and tolerability while facilitating enhanced delivery across the stratum corneum and into the epidermis. Peptides are categorized according to their biological functions, including signal, carrier, and neurotransmitter-inhibitory peptides, which may promote collagen synthesis, modulate matrix metalloproteinases, reduce wrinkle formation, and support skin repair. Particular emphasis is placed on the potential synergistic combination of nano-retinol and nano-peptides within multifunctional formulations to target complementary mechanisms involved in skin aging. Key formulation parameters, including particle size, zeta potential, encapsulation efficiency, excipient compatibility, and physicochemical stability, are discussed in relation to product performance and safety. Advanced evaluation approaches, including in vitro release, ex vivo skin permeation, and clinical studies, are reviewed for assessing efficacy and skin delivery. Safety considerations, including irritation, nanotoxicological risks, and long-term exposure, are also examined. Regulatory perspectives from the US FDA, EMA, and CDSCO are discussed, along with emerging opportunities in stimuli-responsive nanocarriers, AI-assisted formulation development, and personalized nano cosmeceuticals.

KEYWORDS: *Nano-retinol; Nano-peptides; Nano cosmeceuticals; Dermal drug delivery; Controlled release.*

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INTRODUCTION:

The aging of the skin is a progressive physiological process the alterations on the skin's form, functionality and aspect as we age, denoting the influence of interior physiologic as well as environmental external forces. Over time, the skin loses its function of efficiently self-healing, holding hydration and sustaining structure which result in characteristic traits as wrinkling, fine lines, dryness, flaccidity and abnormal skin tonality. Since the skin plays a very important role on body protection, sensibility and temperature regulation, its loss leads not only to aesthetic, but also functional, problems [1]. Skin aging is usually characterized in two types: -intrinsic -extrinsic Intrinsic aging (also known as chronological aging), it's conditioned by genes and natural process of metabolic modifications. This happens even though there are no external influences acting on the skin and is slow progress through the course of time. It mainly involves changes related to hormonal imbalance, decreased cellular regeneration rate, mitochondrial dysfunction and the constant decrease of the telomeres length [2]. Over years, this process reduces the number of fibroblasts cells (collagen and elastin production) and the connective matrix suffers damage, making it decrease and hence decrease skin elasticity and firmness. Skin generally looks dry, thin, and shows wrinkles and fine lines. Extrinsic aging is due to external factors and has been seen as a pre- acceleration of the process of chronological aging. It has been found that that ultraviolet rays from the sun cause it by producing something that is also known as photoaging. Skin is aging also comes about because of such things like pollution, chronic stress, smoking and even poor eating habits, the rays and substances work together to break down cells and keep your skin working normal. Free radicals is what causes skin to become photo-aged because of exposure to the UV rays and environmental pollutant. Free radicals are essentially a reactive molecule; free radical can breakdown the cellular building blocks including lipids, protein and DNA in your skin [3]. ROS is produced in the body normally during the normal course of cell metabolism but during the period of excessive UV radiation exposure to environmental pollution their levels will greatly rise, causing all types of cellular cascade including activation of MMP that breakdown collagen of the skin so when your skin does not contain collagen, the extracellular matrix reduces, and skin begins to form wrinkle. The aging caused by UV radiation happens in a number of ways: The UV ray can penetrate your skin resulting in direct DNA damage; promote skin inflammation and an increase in oxidative stress; affect and disrupt communication between skin cells and expedite the destruction of collagen fibers. The prolonged result of this action over years cause impairment of cells in which proteins get accumulate and the structure of skin is weakened; in the case of pollutants their effects may promote additional free radicals to be created thus promote skin inflammatory reaction in on-going ways [4]. The skin barrier is compromised and small particles, as well as harmful chemicals, can gain entry to increase the risk of oxidative stress and ageing. At a tissue level the ageing skin will present different structural and biological changes: the epidermis becomes thinned and will show a poorer healing potential, due to a decreased rate of turnover of its main cellular component: the keratinocyte. In the dermis, collagen production is greatly reduced whilst pre-existing collagen is degraded. Dry skin and poor skin volume is experienced. The circulation within the skin also decreases thus limiting nutrient availability and delaying healing. In addition, aged skin accumulates senescent cells that remain metabolically active but stop dividing. They secrete a number of inflammatory molecules and enzymes that mediate the breakdown of tissues and thus the chronologic aging of the skin. Based on these processes modern age-defying products will often aim at a simultaneous approach which could include stimulation of collagen production, protection against free radical damage and improvement of the penetration of ingredients into the skin[5]. Skin aging happens as a result of intrinsic and extrinsic mechanisms as demonstrated in **Fig. 1.** Intrinsic aging is related to chronological and genetic aging as well as hormone changes, while extrinsic aging has more to do with environmental factors like exposure to ultraviolet rays, pollution, and smoking. All of these contribute to an increase in the amount of reactive oxygen species and oxidative stress, leading to the induction of matrix metalloproteinase that promotes collagen breakdown. This leads to progressive degradation of the extracellular matrix and hence wrinkling and fine lines[6].

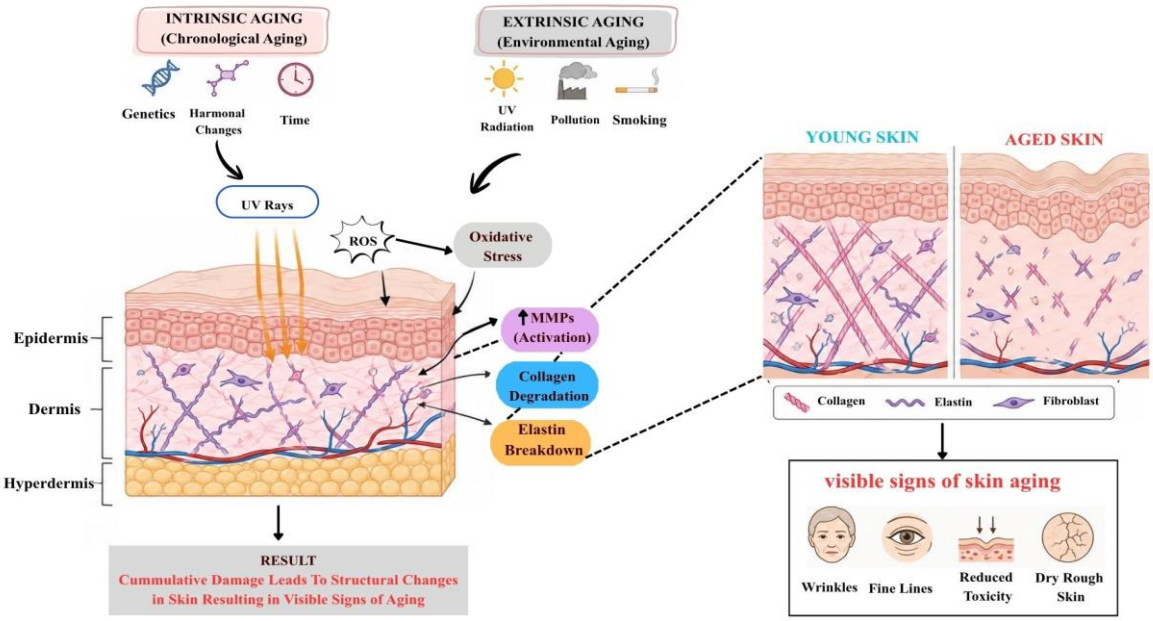


Figure 1: Schematic overview of intrinsic and extrinsic mechanisms of skin aging, highlighting the contribution of chronological factors, environmental stressors, oxidative stress, matrix metalloproteinase activation, collagen degradation, and elastin breakdown[7].

CONVENTIONAL ANTI-AGING APPROACHES AND THEIR LIMITATIONS

RETINOIDS IN ANTI-AGING THERAPY

Retinoids are compounds of vitamin A which have become widely utilized by dermatologists as treatments that are known to reverse and prevent skin aging processes. Retinoids exist in various forms including retinol, retinaldehyde, and retinoic acid and they vary in terms of effectiveness and the manner in which they are converted into an active compound in the skin. Retinoids have been designated as the most efficacious products available for use to treat fine lines, and wrinkles as well as a general increase in a more youthful looking complexion. Retinoids work by regulating genes and influencing cellular processes within the skin. The mechanism of action is based on the ability of retinoids to penetrate into the skin's epidermis and are subsequently converted to an active form (retinoic acid) by enzymes present in the skin[8]. The retinoic acid is subsequently able to bind to special cellular receptors named retinoid acid receptors (RARs) and retinoid x receptors (RXRs) that act as transcription factors to regulate specific gene transcription that play role in proliferation and differentiation of the cells and repair of the tissue. By doing so, retinoids stimulate proliferation of keratinocytes in the epidermis thereby enhancing turnover rate in epidermis and thereby eliminating old keratinocytes with newer healthy cells. Among the major functions of retinoids in the context of antiaging therapies include the regulation of collagen production. Collagen is a structural protein that strengthens and firms the skin. Collagen production diminishes as we age, and our retinoid treatment plan encourages your body to make more collagen while preventing breakdown[9]. Restoring the structure and strength of your skin's matrix, this combined action will decrease the appearance of fine lines and wrinkles. Furthermore, retinoids have the ability to positively affect melanin production and even out your skin tone. They will redistribute skin pigment granules and reduce pigmentation so they are appropriate for treating age spots and the other irregular skin pigmentations caused by photodamage. Retinoids will also indirectly increase your skin's moisture content. They do this by stimulate production of hyaluronic acid-like substances known as glycosaminoglycans that can attract water into skin cells and bind water to the skin's surface. While effective, traditionally, retinoids were associated with various side effects including red and dry skin and skin peeling or flaking, which was more likely to occur when you were first starting to use the medication. The latest prescription products have been developed to make the use of retinoids as comfortable as possible while not diminishing their ability to provide results[10].

PEPTIDES IN TRADITIONAL SKINCARE

Even though Peptides are essential for Anti-aging skincare products, their conventional way of delivery causes various issues that lower down the efficacy of products: - Instability- The peptides are sensitive to the environment (temperature, pH, light) and may undergo some structural alterations and get lose their functional property on their storing period or even during their application time, making their efficacy difficult to preserve in common product formulation [11]. Enzymatic Degradation- When peptides applied to skin, it gets in contact with the

proteolytic enzyme present on surface of skin and on inner skin tissues and may get fragmented before it reaches the specific site of action thereby decreasing it effective functionality by some order of magnitudes as a small fraction of it can act to give a Biological response. Poor Bioavailability-Peptides have limited bioavailability to penetration through the stratum corneum. It is difficult for them to penetrate due to hydrophilic nature of molecules and relatively higher molecular size in comparison to small molecules[12]. As highlighted in **Table 1**, nanofomulations of retinol and peptides have certain advantages over traditional formulations in respect of stability, skin penetration, irritability, bioavailability, release, and effectiveness. The use of nanocarriers in these systems can be more protective for the drugs as well as help in controlled release[13].

TABLE 1: COMPARISON OF CONVENTIONAL RETINOL/PEPTIDE AND NANO-RETINOL/NANO-PEPTIDE FORMULATIONS BASED ON KEY PHYSICOCHEMICAL AND PERFORMANCE PARAMETERS.

Parameter	Conventional Retinol/Peptides	Nano-Retinol/Nano-Peptides
Stability	Low (sensitive to light, heat, oxygen)	High (protected by nanocarriers) [14]
Skin Penetration	Limited (barrier of stratum corneum)	Enhanced (deep dermal delivery)[15]
Irritation Potential	High (redness, peeling)	Reduced (controlled release)[16]
Bioavailability	Low	High[17]
Release Profile	Immediate	Controlled and sustained[18]
Therapeutic Efficacy	Moderate	Improved and targeted[19]

NANOTECHNOLOGY IN ANTI-AGING PRODUCTS

NANOTECHNOLOGY IN COSMECEUTICALS

Nanotechnology in Cosmetics Nanotechnology as revolutionary tool in the realm of cosmeceuticals. The cosmetic products that we use regularly on our skin have certain shortcomings and a lot of research has been going on to address these. One such innovation has come in the form of the nanotechnology or nanomedicine which can resolve various limitations of the existing formulations. The field of nanotechnology is concerned with the creation, characterization, fabrication, and application of materials at very small scales ranging from 1 to 100 nanometres. Nanomaterials at nanoscale display remarkable new physic-chemical properties as the result of high surface to volume ratio and unique electronic, optical, physical and chemical behaviour. The key factors responsible for such improvements in skin penetration using nanotechnology lie in the improved and well-regulated transportation of the actives within the deeper layers of skin[20]. There exists a natural stratum corneum of our skin which prevents the absorption of most regular products. Thus, nanocarriers in this cosmetic technology provide targeted delivery to the deeper skin layers allowing efficient interaction and providing a controlled release of the active ingredients. The different nanocarriers that are applied in cosmetic products include the following; Liposomes, Noisome Solid lipid nanoparticles (SLNs) Nanostructured lipid carriers (NLCs) Nano emulsions polymeric nanoparticles. Because many active ingredients such as retinol and peptides are highly sensitive to various environmental elements including light, oxygen and temperature[21]. Microencapsulation helps to avoid the degrading of ingredients to ensure their longer shelf life and maintaining biological efficacy. Nanocarriers also offer prolong and controlled release of the active substance to provide better functionality and a wider scope for product usage in turn lessening application rates. One more important advantage, the bioavailability of active ingredient through skin. With nanoscale the penetration is enhanced since it has larger surface area and it penetrates into stratum corneum through intercellular space or hair follicle. Moreover, the nanotechnology enhances sensorial properties like texture, spreadability, and aesthetic look[22].

TYPES OF NANOCARRIERS USED IN SKINCARE

Nanocarriers used in modern skin care are important for the optimal delivery of active compounds to the skin. These nanostructures have been developed to achieve improved stability, controlled penetration and release of active compounds. Various classes of nanocarriers are employed in cosmeceuticals. Liposomes- a very common nanocarrier for cosmetic and drug delivery applications is the structure consist of an enclosed cavity surrounded by at least one phospholipid bilayer structure that are similar to that of cellular membranes. Liposomes encapsulate hydrophilic and lipophilic drugs and serve as the adaptable drug delivery systems. Its biocompatibility and ability to fuse with cell lipids facilitate delivery of the incorporated agents[23]. Niosomes are vesicles comprised of non-ionic surfactants that serve the purpose for encapsulation as liposomes but are less costly to prepare and show greater stability. They have shown good enhancement of drug retention and minimal absorption through the systemic circulation. Solid lipid Nanoparticles (SLNs) contain solid lipid material which is stable at room and physiological temperature. These carriers provide controlled release and safeguard sensitive material. NLC's are

very suitable for carrying lipophilic cosmetic agents such as retinol. Nano emulsions are unstable O/W or W/O emulsions whose droplets size is in Nano-meter range, their main application is to increase solubility of relatively hydrophobic material and their spreading capability, small droplet size provides efficient absorption and guarantee homogeneous distribution, biodegradable polymeric nanoparticles could allow control release of encapsulated substances[24]. As it is evident from **table 2**, different kinds of nanocarriers have unique composition and functions that can be utilized in the application of anti-aging products. Different nanocarrier systems can offer a variety of benefits such as better penetration, better stability, controlled release, higher drug loading, higher solubility and targeted delivery[25]. As demonstrated in **fig. 2,** several kinds of nanocarriers have been studied to improve topical delivery and penetration of bioactive substances into the skin. The kinds of nanocarriers studied include liposomes, noisome, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions, and polymeric nanoparticles. These different kinds of nanocarriers differ not only in composition but also in internal structure, being either vesicles based on phospholipids or surfactants, or solid or mixed lipid matrices, oil-based nanoemulsions and polymeric systems[26].

TABLE 2: TYPES OF NANOCARRIERS USED IN ANTI-AGING FORMULATIONS AND THEIR PRINCIPAL FUNCTIONS.

Nanocarrier Type	Composition	Function in Anti-Aging
Liposomes	Phospholipid bilayer	Enhances penetration & biocompatibility[27]
Niosomes	Non-ionic surfactants	Improves stability & drug retention[28]
SLNs (Solid Lipid Nanoparticles)	Solid lipids	Controlled release & hydration[29]
NLCs	Solid + liquid lipids	High drug loading & stability[30]
Nanoemulsions	Oil-water dispersions	Improves solubility & spreadability[31]
Polymeric Nanoparticles	Biodegradable polymers	Targeted and sustained delivery[32]

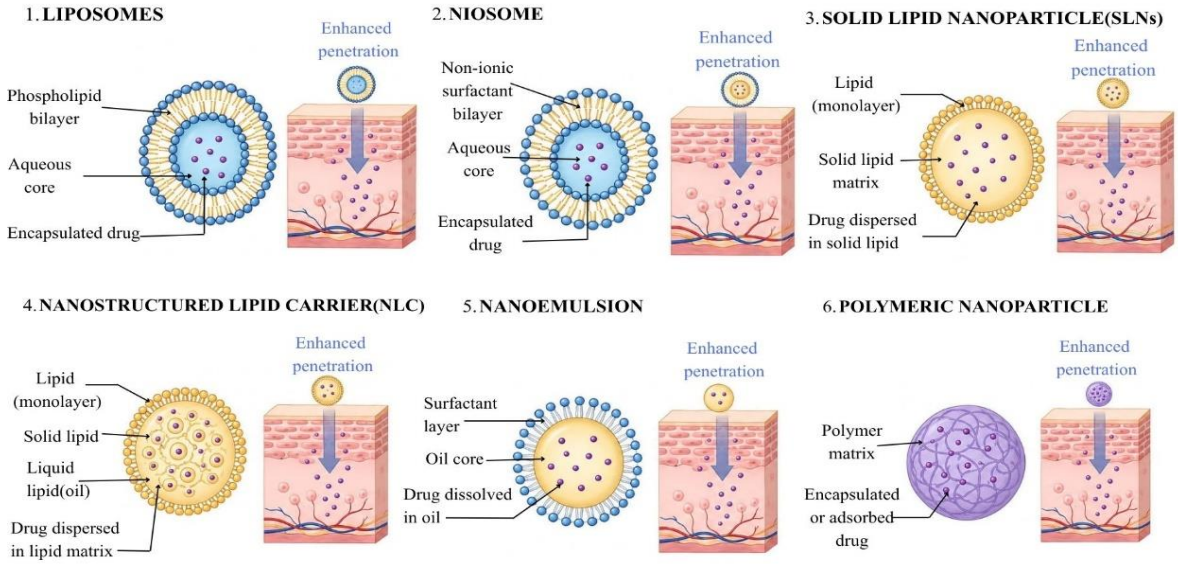


Figure 2: Schematic comparison of major nanocarrier systems for enhanced dermal delivery, including liposomes, niosomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, and polymeric nanoparticles[33].

NANOTECHNOLOGY IN ANTI-AGING FORMULATIONS

Benefits of nanotechnology in the design of anti-aging cosmetic products Nanotechnology provides a number of very useful benefits for the design of anti-aging cosmetic products and is therefore an indispensable element in the contemporary study of cosmetic. One such important benefit is increased penetration of active ingredients into the skin. The skin is covered with an outer protective barrier that acts as an inhibitor to penetrate any traditional cosmetic formula - stratum corneum. Because the nanocarrier is so small, it is possible to engage it much better with this barrier, facilitating penetration to the deeper layers where their biological activity can then take place[34]. Other important benefit: Enhanced stability of labile ingredients many ingredients used in cosmetic antiaging preparations such as retinoids, peptides deteriorate rapidly in the presence of heat, light or air; in other words, they are

not very resistant. Encapsulating them in nanoparticles protects them against adverse conditions and allows the chemical stability of the preparation to be maintained throughout its lifetime, even under challenging external conditions. Controlled and slow release of active ingredients[35]. The controlled and timed release allows active ingredients to be gradually released into the skin over time. Nanocarriers act to provide a sustained release of active ingredients, rather than an intense release all at once, which is especially advantageous for powerful ingredients like retinoids which can cause sensitive irritation at high doses. Enhanced absorption. Another benefit of nanocarriers is the provision of enhanced bioavailability. Nanocarriers increase the solubility of poorly water-soluble active ingredients and interaction of the actives with skin cells, resulting in greater bioavailability, and greater penetration of ingredients leading to more impressive ant aging results[36].

NANO-RETINOL IN ANTI-AGING

CONCEPT AND DESIGN OF NANO-RETINOL

Nano-retinol is the inclusion of retinol into a nanostructure to achieve stability, increase penetration and to make use of anti-aging benefits. Although commonly used and potent, traditional retinol has the following limitations including instability, low penetration through the skin and irritation to the skin. Nano-retinol systems were developed to overcome this problem through the use of nanotechnology-based delivery systems designed to carry and deliver retinol into deeper layers of skin while protectively encapsulating retinol from degradation. Development of Nano-retinol systems: Creation of such nano-retinol systems may require encapsulating retinol into the nanocarriers like liposomes, SLN (solid lipid nanoparticles), NLC (nanostructured lipid nanoparticles), Nano emulsions or polymeric nanoparticles etc[37]. All these carriers were chosen depending on their compatibility with retinol. As Retinol is unstable under light, heat and oxygen conditions, the use of the nanocarriers would protect retinol from its breakdown and it would remain stable in chemical manner during the period of storage and usage of nano-retinol system. Another feature in development of nano-retinol systems includes: Enhanced particle size in such delivery system nanocarriers would generally design in size range of 10-200nm to get interact effectively with the barrier skin as these particles would have a tendency to follow pathways, intercellular or intra follicular pathways into deeper layers[38]. This in result makes retinol to deliver in the deeper layers i.e epidermis and dermis for increasing their anti-aging activities. The nanocarriers may be additionally modified with other ingredients in formulation of nano-retinol like some of biocompatible lipids and polymers which promote binding of formulation to skin, enhancing permeability and improve the absorption. Furthermore, some delivery systems will respond to changes in temperature or PH on the skin and deliver retinol on that target condition. Therefore, the principal behind the designing and formulation of Nano-retinol aims at increase in penetration, enhanced bioavailability and to overcome drawbacks of simple retinol[39].

MECHANISM OF ACTION OF NANO-RETINOL

Nano-retinol anti-aging benefits. It offers the same anti-aging benefits as conventional retinol, but at an accelerated rate. When applied to the skin, the nanoscale delivery system in Nano-retinol helps to better facilitate deep penetration of retinol through the stratum corneum layer of the skin. This helps to deliver the retinol more evenly throughout the epidermis and dermis of the skin, ensuring a larger amount of the active ingredient can penetrate where it needs to. Once penetrated into the skin, the retinol enzyme conversion process turns retinol into retinaldehyde and finally the bioactive form, retinoic acid. Retinoic acid works by activating specific nuclear receptors; retinoic acid receptors (RARs) and retinoid X receptors (RXRs). This is a process which regulates the expression of genes which govern cell proliferation, cell differentiation and the formation of the extracellular matrix[40]. It, therefore, accelerates keratinocyte turnover, allowing for the shedding of the damaged surface skin cells, and for the generation of newer and younger skin. It stimulates fibroblasts in the dermis to increase production of collagen and elastin fiber while at the same time inhibiting matrix metalloproteinases (MMPs) which break down collagen. In both ways it restores support to skin structure and also smooths out the appearance of fine lines and wrinkles. Finally, it improves melanin dispersion on the skin[41]. As depicted in **fig. 3**, the encapsulation of retinol in liposomes can enhance the delivery of the compound to the skin through its easy penetration and release from the liposomes. Once the retinol is delivered to the epidermis and dermis layers, it will be converted into retinoic acid by the enzymes present in the skin cells. Retinoic acid is able to activate the retinoid-dependent signalling pathways and thus increase the function of the fibroblasts in producing extracellular matrix. This can promote the formation of type I and type III collagen and elastin, which can help in organizing the dermis layer of the skin and reduce wrinkles[42].

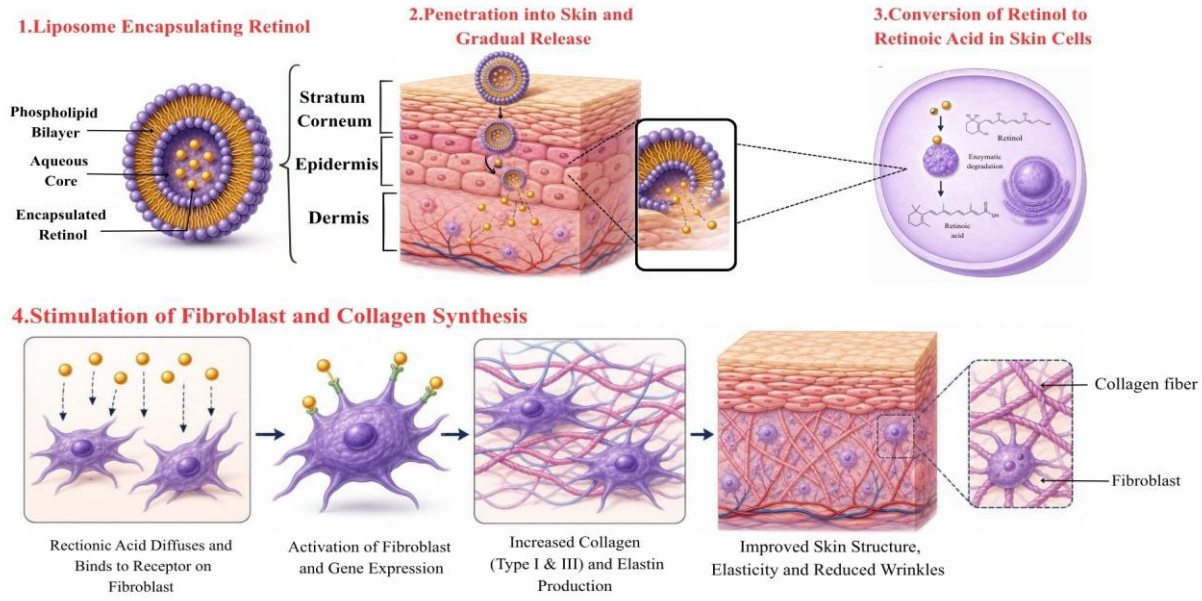


Figure 3: Schematic representation of the proposed anti-aging mechanism of nano-encapsulated retinol, showing liposomal encapsulation, skin penetration and gradual release, conversion of retinol to retinoic acid, fibroblast activation, and stimulation of collage[43]

BENEFITS OF NANO-RETINOL OVER CONVENTIONAL RETINOL

There are a number of benefits of nano-retinol compared to traditional retinol, including Nano-retinol, which is considered superior to traditional retinol as part of many current age-reversal compositions. Retinol degrades readily from contact with various environmental conditions including exposure to light, oxygen, and heat. The utilization of nanocarriers for encapsulates of the retinol is helpful in protecting retinol from any external effects thereby enabling efficient use of retinol in various applications[44]. Higher penetration through skin barrier of retinol as against conventional retinol is yet another key feature of retinol that works through skin. Conventional retinol is relatively unable to get through the skin's stratum. Nano- retinol can penetrate deeper through skin barrier thereby reach the destination layer to act on the targets effectively. Less skin irritant, as typical retinol-based cosmetics often cause dryness, itching, or even peeling, nano-retinol causes gradual release to the active form and this minimises the exposure to retinol, making it suitable for people with very sensitive skin type[45].

NANO-PEPTIDES IN SKIN REJUVENATION

CLASSIFICATION OF PEPTIDES

Anti-aging peptides are classified into several categories depending on their specific biological roles and mechanisms of actions. This classification of peptides can provide useful information on their specific effects on the health of the skin and in turn the reduction of visible aging effects. Among the many types, the signal peptides are the most common ones used in cosmeceuticals. The signal peptides signal the fibroblasts to synthesize the vital structural elements of the skin including collagen, elastin and fibronectin[46]. This production enhances elasticity and smooths wrinkles. The carrier peptides carry and transport minerals to the skin. These minerals facilitate enzyme functions involved in tissue repair, such as copper and magnesium. Copper peptides have wound healing and elasticity improving benefits. Peptides inhibiting neurotransmitter actions are sometimes called "Botox-like" peptides, as they inhibit the muscles' contracting action[47].

MECHANISM OF ANTI-AGING ACTION

The anti-aging effect of peptides results from multiple mechanisms involved in skin repair and regeneration. When topically applied, peptides are capable to penetrate the stratum corneum and bind to the receptors and other targets present in the cells. Owing to their small molecular size they are very effective signalling molecules able to initiate signalling cascade in the skin cells. An important process is increasing collagen production. Peptides stimulate the fibroblast to produce more collagen and elastin which give the skin its firmness and elastic properties and so reduce fine wrinkles. Furthermore, they enhance skin barrier by stimulating synthesis of proteins and lipids which build up the epidermis, thus maintain skin moisture and guard against environmental damage[48]. Additionally, some peptides exhibit anti-inflammatory effects which means they calm the skin and reduce the redness and so accelerate healing of skin injury. Lastly, they can act as inhibitors of

collagen degradation. Nano-encapsulation dramatically increases the efficacy of peptides within anti-aging product formulations. Increased Stability One major benefit of nanoencapsulation is improved peptide stability. Peptides are highly susceptible to degradation caused by external forces and enzymatic activities in the body, but when encapsulated within nanocarriers, peptides are protected from such effects and will remain potent and effective. Enhanced Skin Penetration Peptides normally have difficulty to penetrate the outer layer of the skin due to their water loving characteristics. The nanocarrier delivers the peptides through the stratum corneum and into deeper skin levels where they can have their impact. Controlled and Prolonged Release One other main advantage of encapsulation is a timed release of peptides[49,50]. As shown in **figure 4**, the mechanism for the nano-encapsulation of bioactive peptides includes the process of encapsulating bioactive peptides in nano-systems, their penetration into the skin, cellular uptake and controlled intracellular release. Released peptides will be able to interact with cellular receptors and trigger signalling pathways that will lead to fibroblast function activation and extracellular matrix production. Further stimulation of collagen and elastin synthesis will help increase skin elasticity and structure, reduce the appearance of wrinkles. Generally speaking, bioactive peptides can be classified into three main groups: signal peptides, carrier peptides and neurotransmitter blocking peptides[51].

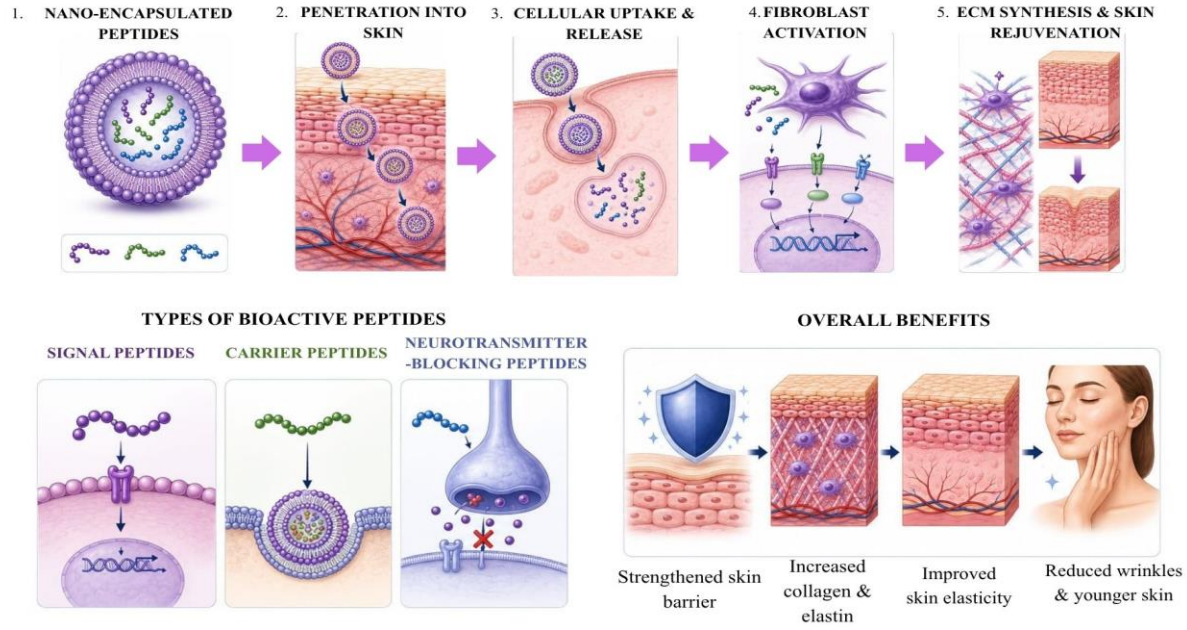


Figure 4: Schematic representation of the proposed mechanism of nano-encapsulated bioactive peptides in skin rejuvenation, including nano-encapsulation, skin penetration, cellular uptake and release, fibroblast activation, and subsequent extracellular matrix synthesis[52].

FORMULATION AND DELIVERY STRATEGIES

ENCAPSULATION TECHNIQUES

Encapsulation is an important technique for preparation of Nano-retinol and nano-peptide systems to facilitate transport of the active principles. The term encapsulation is referring to entrapping or incorporating an active compound into nanoscale carrier to increase its skin penetrability, avoid degradation in the surrounding environment, and achieve desired release profiles of active ingredients. Depending on the characteristics of the drug substance and specific requirements of the drug formulation, the following encapsulation strategies were explored: thin-film hydration, solvent evaporation, high pressure homogenizer and micro fluidization[53]. Thin-film hydration, for example, has been explored for preparation of liposomes which contains active ingredients entrapped within multilamellar or unilamellar vesicles which are formed by hydrating a thin lipid film. Solvents are used to dissolve polymer and drug and are subsequently evaporated, forming nanoparticles. High pressure homogenizers are commonly used for preparing SLNs (solid lipid nanoparticles) and nano-emulsions to provide uniform particle size and dispersion[54].

Controlled and Sustained Release Systems

To maximize the efficacy of nano-formulated anti-aging cosmetics, their controlled, sustained release to the skin must be implemented. As the opposed to a single, bolus release of active compound, an extended, regulated release provides and maintains therapeutic drug concentration in target compartment over longer period of time that ensures better efficacy and leads to decreased likelihood of side effect development. In case of such compounds as nano-retinol and nano-peptides, controlled release is performed by tailoring the composition of nanocarriers, thus controlled release of the

encapsulated substance depends on the kinetics of release/degradation of the vehicle[55]. Polymeric nanoparticles slowly release their content during time based on the degradation of polymer matrix whereas for lipid-carriers, a diffusion-assisted release mechanism comes into play for active compound as they move from the lipid interior through lipid structures. This approach will be especially useful for high potency, irritating actives, like Retinol that cannot be delivered simultaneously to an increased dose that can, for instance, induce retinoid dermatitis. Also, it's known that systems that are longer available in the body have higher patient compliance[56].

STABILITY ENHANCEMENT APPROACHES

Stability can be essential when producing our Nano-retinol and nan-peptide formulations, given these highly sensitive compounds could lose some benefit through the different environmental elements encountered over time. Certain ways have been developed, so they stand in our formulas for longer and have no trouble performing throughout our usage. By way of example, encapsulation can shield ingredients such as these actives from photo-degradation and the damaging results of air and changes in temperature[57]. As can certain anti-oxidants such as Vitamin E and ascorbic acid incorporated within our formula. Proper packaging also adds stability, for example light proof airtight containers. Changing a variety of other formulation parameters such as ph. pH changes to have influence on the overall stability of peptides and retinol[58].

EVALUATION OF NANO ANTI-AGING SYSTEMS

PHYSICOCHEMICAL CHARACTERIZATION

Physicochemical characterization is critical to developing Nano-based anti-aging product. It determined the stability, quality and efficiency of the nanocarrier formulation. Among physicochemical characteristic important: Particle size the particle size of nanocarrier should be in the range of 10 to 200 nm, because small particle size will improve the skin Penetration and distribution of active ingredients uniform in the formulation. DLS is normally used for particle size analysis. Zeta Potential Iis measurement of charge on surface of nanoparticles, predicting the physical stability of the product, A high zeta potential (absolute value) indicates the repulsion between the nanoparticles resulting in good stable dispersion, the higher the zeta potential (absolute value) may correlate with better stability of the formulation[59]. Morphological characterization Evaluation under TEM, and scanning electron microscopy, used to measure shape and structure of the nanoparticle. Encapsulation efficiency % of active agent entrapped inside the nanocarrier. It reflects amount of active ingredient delivered and prevents over dosage or waste costly active formulation (such as retinol, peptide). Also, other parameters pH, viscosity, Drug Release are analyzed to be consistent with expected skin compatibility and performance. The developed nano anti-aging system was evaluated using a range of physicochemical and performance parameters to establish its stability, structural characteristics, drug-loading capacity, release behavior, and skin delivery potential. The major evaluation parameters, corresponding analytical techniques, and their significance are summarized in **Table 3**[60]

TABLE 3: EVALUATION PARAMETERS OF THE NANO ANTI-AGING SYSTEM

Parameter	Method/Technique	Significance
Particle Size	Dynamic Light Scattering (DLS)	Determines penetration efficiency[61]
Zeta Potential	Electrophoretic analysis	Indicates formulation stability[62]
Morphology	TEM / SEM	Defines shape & structure[63]
Encapsulation Efficiency	Spectroscopic methods	Drug loading capacity[64]
Drug Release	In vitro diffusion studies	Controlled release behavior[65]
Skin Permeation	Franz diffusion cell	Measures dermal delivery[66]

IN VITRO STUDIES

In vitro research is extremely beneficial in deciding whether a specific Nano formulation works in the laboratory, before experimenting upon animals and or human. In a laboratory or in vitro experimentation an approach is usually experimented over cell cultures and tissues. Skin permeation and penetration study where the nanocarrier facilitates drug penetration into the strata corneum is evaluated using models (like Franz diffusion cell)[67]. The drug release from the nanocarrier system determines whether the product controls the release pattern to minimize side effect on exposure and optimize on efficacy of drug on skin. Cytotoxicity of the formulated cream or lotion over skin cells, i.e. Fibroblasts or keratinocyte is determined through methods like MTT assays. Antioxidant and anti-aging properties studies may also be conducted, to determine its function in destroying free radicals and helping collagen synthesis respectively and provides key indications for bio efficacy of the formulated product[68].

IN VIVO AND CLINICAL EVALUATION

It is important that an in vivo, and, subsequently a clinical study be carried out before using Nano anti-aging product for efficacy. Animal studies, usually

in vitro are performed so that to obtain Information about skin irritancy, acute toxicity, and possible Pharmacological effects. Some Information can be deduced about interactions between Formulation And tissues. Then A formulation proven to be safe and Effective in vitro undergo Human clinical trials. The formulation is applied in vivo or in situ to various subjects for a specific period of time. Changes in various Parameters are measured such as improvement of wrinkle, increased firmness of skin, increased moisture, improve color of the skin, etc. These studies are also performed to provide a rational basis for topical skin aging Products And evaluation using some non-invasive measurement methods such as corneometry, cutometry, imaging of skin etc. Regular patch Tests are performed for irritating and allergic potentials. Long term continuous benefit-risk assessment can also be performed [69–71].

SAFETY AND REGULATORY ASPECTS

TOXICOLOGICAL CONSIDERATIONS

Toxicological analysis is an important consideration when designing nano-based anti-aging products because there may be potential safety issues associated with the intrinsic properties of the nanomaterials that were selected. Through their size, nanoparticles can enter deeper into the skin and sometimes have a presence in the blood. There may be unknown effects of the nanoparticle-biological interaction as nanoparticles can affect cells at the cellular and even molecular level. A factor, which was mentioned previously is cytotoxicity: whether the nanoparticles are capable of inducing cell death or altering the normal functioning of skin cells (keratinocytes or fibroblasts)[72]. Some nanomaterials induce oxidative stress in the cell through the production of ROS leading to damage of cells. It is therefore vital to determine the oxidative potential of Nano formulations as this can induce a multitude of undesirable effects. Irritation and sensitization are also an important consideration. While nano-carriers are meant to limit irritation of the skin it is possible that they, or the amount of active ingredients within, can produce redness of the skin, or an allergic reaction (irritation or sensitization)[73].

REGULATORY GUIDELINES (FDA, EU, CDSCO)

Regulation of Nano-enabled cosmeceuticals is necessary to ascertain safety, quality and efficacy of these products. Regulatory systems for cosmetics, and indeed Nano-enabled cosmetic products, exist in various regions of the world. In the United States of America, regulation of cosmetics falls under the jurisdiction of the Food and Drug Administration (FDA) according to the provisions of the Federal Food, Drug, and Cosmetic Act. At the moment there is no particular law that exclusively governs nanomaterials within cosmetic products in the US but regulations insist on manufacturer safety and correct labelling[74]. The use of nanotechnology, on the other hand, must be sufficiently supported by safety data of the product. Cosmetics within the EU are governed by the EU Cosmetics Regulation (EC) No. 1223/2009, which defines specific provisions for nanomaterials. Manufacturers are compelled to disclose the list of ingredients in nanoform to the authorities concerned along with safety data. Pre-market notification and safety evaluation of cosmetics containing Nano ingredients is mandatory in EU. Cosmetics in India are regulated by CDSCO under the Drugs and Cosmetics Act[75].

CHALLENGES IN APPROVAL

There are numerous hurdles that must be overcome, despite rapid progress, in the regulatory approval of Nano-enhanced anti-aging products. One of the main problems is that there are no standard testing methods and assays used in order to determine the safety of nanomaterials in relation to Nano-enhanced anti-aging product efficacy. The data generated may be confusing when tried to equate traditional testing methods with Nano-scale ones. Another great problem involves long-term safety issues. The effects of long-term skin exposure and of long-term systemic toxicity from nanotechnology in cosmetics have not been studied in enough depth, due to the infancy of nanotechnology in cosmetics, and it may take a longer, and ultimately more expensive, time to get regulatory approval. Lastly, there are complications associated with a manufacturer when wanting to market the same product globally. The regulations concerning the FDA, EU, and CDSCO vary and this leads to more complications regarding the approval and marketing of product[76,77].

FUTURE PERSPECTIVES

In this field the impact of nanotechnology has moved forward over the years for instance use of nanomaterials in the development of Nano-retinol and Nano-peptides has made a lot of advance progress for dermatology and cosmeceuticals future. Due to advancement in our knowledge of science and technology in future some breakthrough innovations can bring innovative methodologies for more efficient, secure, safe and targeted treatment approaches to improve the conditions of aging skin. Most recent advancement to improve drug delivery has the intelligent nanocarriers, these nanostructures are smart so that they can respond to stimuli like change in pH, temperature or activity of the enzyme[78]. Example, Nano-particles that respond to change in the pH can only release active compound in case the formulation encounters a particular pH which the aged skin often presents, which is slightly acidic in relation to healthy skin. Multifunctional nanocarriers are also being constructed to allow simultaneous release of various compounds (retinol, peptides, antioxidants,

vitamins) which could interact synergistically to have better results. Lastly the Artificial Intelligence (AI) and machine learning is also helping in the design of product by predicting their compatibility, retention within skin and activity from huge datasets. Nano cosmeceuticals in near future Nano cosmeceuticals customised According to one's own genetic constitution lifestyle patterns & environmental exposure could be breakthrough during coming years. Environmentally sustainable and green technologies in nanotechnology will also become very significant with the growing awareness for ecological issue[79]. More prolonged in vivo studies are also necessary with regards to potential toxicity by repeated exposure, deposition of these nanotechnological components within or on the skin. Better imaging and analysis techniques will become in use to determine and regulate nanoparticle dynamics within the skin as per its need. Apart from beauty applications; Nano technologies in the field of dermology also have considerable future scope like use of Nano retinol or Nano peptide for certain skin diseases such as hyperpigmentation, acne & other aging disorders because of ability of proper & controlled delivery of medicinal agents. In short, the future seems quite positive for nanostructured anti-ageing preparations focusing on accurate delivery, personalising factor, eco-friendly processes & safety precautions[80].

RECENT ADVANCES AND INNOVATIONS

Nanotechnology has been developing rapidly and changing all segments of the cosmetics industry, among them Anti-age skincare. Nano retinol, nonapeptide, and the recently emerged smart Nano-carriers are major advances in anti-aging skincare nanotechnology. There are smart Nano carriers used to deliver the drug targeted to a particular signal like temperature, pH or biological triggers such as enzymes. For example, pH responsive nanoparticle may deliver drug targeting to sites where skin structure integrity is lost or skin aging is visible. It means more targeted delivery and less systemic exposure/local irritation. Smart Nano carriers may ensure an optimal drug concentration at the target sites with better control. AI in nanotech formulation development[81]. A technological advancement of artificial intelligence (AI) in the formulation of Nano cosmetics is notable. AI can assist in deciphering large dataset consisting of data about biological aspects of the skin, drug chemistry and other physical components, to better model the interactions within Nano formulations, develop novel Nano carrier strategies, optimize nanoparticle characteristics, and select optimal combinations of APIs for anti-aging cosmetics. This expedites the research and development cycle and cuts down the time and costs spent on the conventional trial and error techniques. AI-driven models help predict how products will perform and stabilize under various conditions, resulting in more stable and effectively formulated products[82]. Customized anti-aging skin care represents a rapidly growing and important market thanks to advances in nanotechnology and data analytics. Nano-based delivery systems are extremely important in this development as they allow the amount and type of active ingredients to be controlled accurately. For example, the formulation may be customized for higher levels of peptide content to facilitate collagen building, or low dosage of retinol on sensitive skin. Such individualisation would create both increased treatment effectiveness and higher customer satisfaction. Overall, these advancements are moving the entire anti-aging skincare into a more targeted and efficient and personalized direction. The implementation of smart delivery systems, AI-driven formulation techniques and customized treatment approach has become a monumental advance in the approach to upcoming cosmeceutical products [83].

CONCLUSION:

The increasing demand for efficient anti-aging products has enabled various advancements to cosmeceutical R & D as a result of use of nanotechnology. This review aims to focus upon Nano- retinol, and Nano –peptides, being a type of new formulation aimed to tackle the shortcomings and side-effects encountered with using age-old retinol and peptide formulations. The standard anti-aging products (containing retinol, peptides) are effective; nonetheless pose problems like non-stick to molecules as compared with new materials used in it, easy disintegration and enzymic breakdown and adverse effects such as skin irritation. Therefore, the advent of nanoscale is a strategy for such disadvantages that helps to resolve and enhance overall safety and efficiency. Nano-retinol works effectively by a process of better delivery, protection to molecules from the environment and by gradual release which means, better absorption2; protection from adverse effects and increased biological activity, more production of collagen with reduced irritation and cell regulation, to which Nano-peptides contributes by offering improved stability and bioavailability; as a signalling molecule, helping to make faster recovery of skin tissue, increasing elasticity and reducing visible aging . Moreover, with application of the two nanomaterials (Nano-retinol with nonapeptides together) makes enhancement of anti-aging effect more efficiently to various aging criteria as against a conventional age like degradation of collagen; oxidative damages & inhibition in cell proliferation. Various kinds of nano-carriers i.e. Liposomes, niosomes, solid lipid Nano particles and Nano emulsions have also played the role in revolutionizing topical medication.

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