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Nanotechnology Use with Cosmeceuticals

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The skin is a complex organ and its aging is a complex process. Cutaneous aging is influenced by factors such as sun exposure, genetics, stress and the environment. While skin laxity, rhytides, and dyschromia appear on the surface, these processes originate in deeper layers including the dermis and subcutaneous tissues. Until recently, most topical skin treatments were applied to, and consequently only affected the skin surface. Skin care has evolved to be scientifically based, and as knowledge increases about the physiology of the skin, novel methods of maintaining its health and appearance are developed. New generation skin care products are targeting multiple aging mechanisms by utilizing functional active ingredients in combination with innovative delivery systems.
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Cosmeceuticals represent a new category of multifunctional products that rely on science and technology to deliver clinically proven active ingredients to the skin. Cosmeceuticals are often formulated with pharmaceutical-type active compounds and demonstrated to achieve multiple cell-protective effects for rebuilding healthy skin on a cellular level.[1] For these active compounds it is important that their unique functional characteristics are preserved, which is often a challenge that requires new formulation strategies. Implementation of nanotechnology and advanced engineering proves to be effective in enabling innovative formulations and product solutions. This article describes how the nanotechnology in combination with the new active ingredients enhances the efficacy and tolerability of cosmeceutical products.

Novel Strategies for Skin Protection

Strategies for skin protection are generally formulated by the use of 2 types of agents. Low-molecular-weight molecules, such as ascorbate (vitamin C), tocopherols (vitamin E), ubiquinols (coenzyme Q), lipoic acid, and glutathione are all capable of participating directly in redox reactions and are effective at scavenging reactive oxygen and nitrogen species. In performing these protective functions, they are necessarily sacrificial and must either be regenerated or replaced by supplemental exogenous supplies. More recently, it has been recognized that other molecules that function via indirect mechanisms can also be used to enhance skin protection.[2,3] Such molecules may be direct antioxidants as well, but in their indirect mode of action they induce a multiplicity of cell-protective actions that involve up-regulation of the body's own endogenous antioxidant and anti-inflammatory pathways. The advantage of this indirect mechanism is that the components of the endogenous pathways form an extensive list of proteins and enzymes that function as catalysts rather than reactants and survive far longer than the low molecular weight inducers. By inducing these multiple protective pathways, the molecules that act via this second, indirect mode allow the body to defend itself against multiple mechanisms of tissue damage. The effects of such molecules are therefore pleiotropic rather than more narrowly targeted and, equally noteworthy, their action is sustained rather than transient.

It has only recently been appreciated that the list of indirect cell-protective agents includes many low-molecular-weight compounds previously thought to be only direct antioxidants. Examples of such compounds that are now known to have pleiotropic indirect cell-protective effects include polyphenols, such as the green tea catechins,[4] pome-

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granate ellagitannins,[5] and proanthocyanidins found in several common berries.[6] Other similar molecules containing multiple polyhydroxylated aromatic rings that achieve similar indirect multiple cell-protective effects include the flavones and isoflavones,[7] the gallotannins,[8] and isothiocyanates derived from cruciferous vegetables like broccoli.[2]

Studies on the mechanisms of action of this apparently diverse list of compounds have come together on the observations that they can all target zinc-binding proteins. Such proteins include the matrix metalloproteinases (MMPs), enzymes identified in several examples of connective tissue destruction, and components of the complex nuclear factor-κB proinflammatory pathway that targets increased expression of multiple destructive proteins and enzymes. MMPs and the nuclear factor-κB pathway are inhibited by these compounds, whereas another cysteine-rich, zinc-binding protein, Keap1, is forced by these compounds to release a protein factor, Nrf2, which induces the expression of multiple cell-protective enzymes that regenerate the active chemical forms of the well-known direct antioxidants like ascorbate, tocopherols, and glutathione.[3] Among the most intriguing targets of the pleiotropic indirect cell-protective agents are the histone deactylases, or HDACs. Inhibition of HDAC activity is now recognized as a major mechanism of downregulating inflammation in a wide spectrum of diseases, and most pharmaceutical HDAC inhibitors are noted for their remarkably low toxicity.[9] The natural indirect pleiotropic cell-protective agents listed are also distinctive for their impressive safety and efficacy in HDAC inhibition.[10]

Because many of the compounds listed function via both direct and indirect cell-protective mechanisms, they are potentially at some risk for loss of activity in environments that involve exposure to air and room temperature. Fortunately, strategies are becoming available to protect these molecules from damage from the elements by shielding them in polymeric matrices that are fully biocompatible and can be very rapidly disrupted to release the active payloads directly onto the skin surface. The protection provided by such nanomatrices has a second potential advantage: bioactive agents may be formed in situ on the skin surface by packaging the components that generate the active species in separate nanomatrices. Disruption of the matrices upon application to the skin allows the components to combine and react to produce the desired products without any potential loss of biological activity.

Overview of Skin Delivery Systems

The delivery of active ingredients to skin has earned increasing attention in recent years.[11] A significant number of innovative delivery systems incorporating micro (10^{-6}) or nanostructures (10^{-9}) are being used in skin care with perceptible attributes. The major desired benefits from the use of novel skin delivery systems are (1) improved efficiency of transfer of active ingredients into the target layers of skin, (2) optimal use of high cost active ingredients, (3) improved stabilization of active ingredients, (4) minimization of any skin irritation associated with active ingredients by controlled release, (5) improved ease of application and removal, and (6) improved visible appearance and esthetic quality of the skin after the product is applied. The formulation of a skin delivery system typically involves encapsulation/entrapment of the active ingredient in an inactive matrix via the use of appropriate excipients to obtain the desired outcomes. The major challenges associated with formulation of skin delivery system are loading efficiency, mild processing conditions, and stability/integrity of the formulation to obtain a reasonable shelf life. The major types of skin delivery systems are described in the sections to follow.

Vesicular Systems (eg, Liposomes, Neosomes)

A vesicle is a small membrane-enclosed sac, ranging in size from 15 to 5000 nm that is used for delivery of active substances. Such vesicles are typically formed by bilayer arrangements of amphiphilic molecules with a central core. The active ingredient is typically introduced into the central core at the time of formation. The wide range of vesicular systems used in skin delivery systems can be classified on the basis of the nature of the components used to form the membrane. The core of the vesicular system can be hydrophilic or lipophilic. In addition, vesicles can be classified on the basis of whether the membrane is single walled or multiple walled. Vesicular systems are metastable and the amount of active ingredient that can be loaded is typically $<10\%$.

The most widely used vesicular skin delivery system uses liposomes.[12] Liposomes are spherical vesicles whose membranes most often consist of one or more bilayers of phosphatidylcholine in assemblies in which the hydrophobic nonpolar tails of the amphiphilic phospholipids point inward and the polar headgroups point outward within the lamellar structures. In this system, the hydrophilic active ingredient is encapsulated in the core, whereas the lipophilic active ingredient is encapsulated in the walls of the vesicles. The bilayer structure of liposomes resembles cell membranes in the stratum corneum and thus can penetrate the lipid layers of stratum corneum.

Emulsions (eg, Microemulsions)

An emulsion can be defined as a mixture of 2 immiscible phases, for example, water and oil, with an emulsifier added to stabilize the dispersant droplets. Depending upon the identity of the dispersed or discontinuous phase and dispersing or continuous phase, an emulsion can be classified as a "water-in-oil" emulsion or an "oil-in-water" emulsion. The active substance to be delivered is typically solubilized in the dispersed phase. There are many different emulsion delivery systems differing largely in their structure and viscosity. The most prominent emulsion used as skin delivery system is the microemulsion,[13] a stable transparent or translucent dispersion with a diameter of <1000 nm that is stabilized by an interfacial film of surfactant molecules. Emulsions are ideally

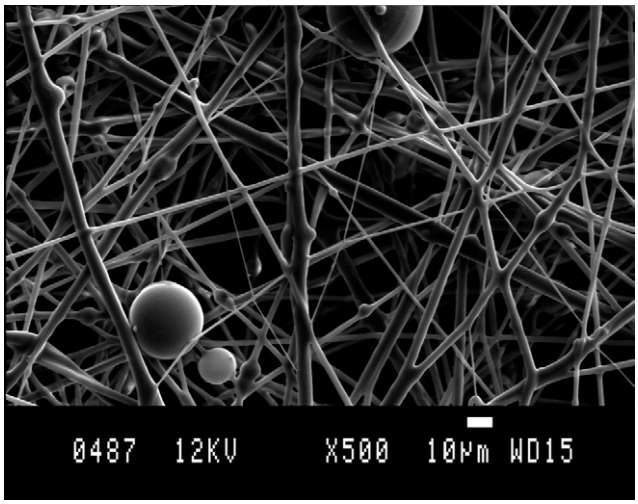

Figure 1 Microscopic image of several cosmeceutical actives incorporated into a nanostructured hybrid delivery system (Agigma, Inc.). Nanostructured hybrids show promise across the multitude of applications due to their ability to accommodate vastly different functional requirements of new generation cosmeceutical active ingredients.

used for active ingredients that are stable in a solubilized state.

Particulate Systems (eg, Solid Lipid Nanoparticles)

These are delivery systems in which the active ingredient is encapsulated or entrapped in a solid state in a solid matrix.[14] Depending upon the choice of the matrix, particulate systems can be broadly classified into polymeric or lipid particles and, depending upon size, can be further classified into micro or nanoparticles.[15] A wide range of polymeric materials have been used for composition of polymeric particles; the resulting structures can cover the spectrum from a continuous shell to an open porous structure. Particulate systems are widely used where the active ingredient to be delivered is not stable in either the solubilized phase or the dispersed phase in emulsions.

The most widely used polymeric particles are the microsponges.[16] Microsponges are uniform, spherical polymer particles, typically 10-25 μm in diameter, that can be loaded with an active agent. These particles subsequently release the active agent through diffusion or after exposure to a selective trigger, for example, moisture or temperature. The unique advantage of this delivery system is its large entrapment capacity, i.e., up to 3 times the weight of the polymer alone. A major disadvantage of the methods most commonly used in forming such polymeric particles is the use of harsh processing conditions, thus limiting their applications to very stable active ingredients that can withstand these conditions that might damage sensitive payloads.

The most widely used lipid particles as skin delivery systems are the "solid lipid" nanoparticles. These solid spherical particles consist of a hydrophobic core of triglycerides or fatty acid derivatives with a relatively high melting point, surrounded by a layer of phospholipids. Advantages of solid lipid nanoparticles over polymeric nanoparticles include the absence of any toxic additives required for polymerization and the biodegradability of the lipids.

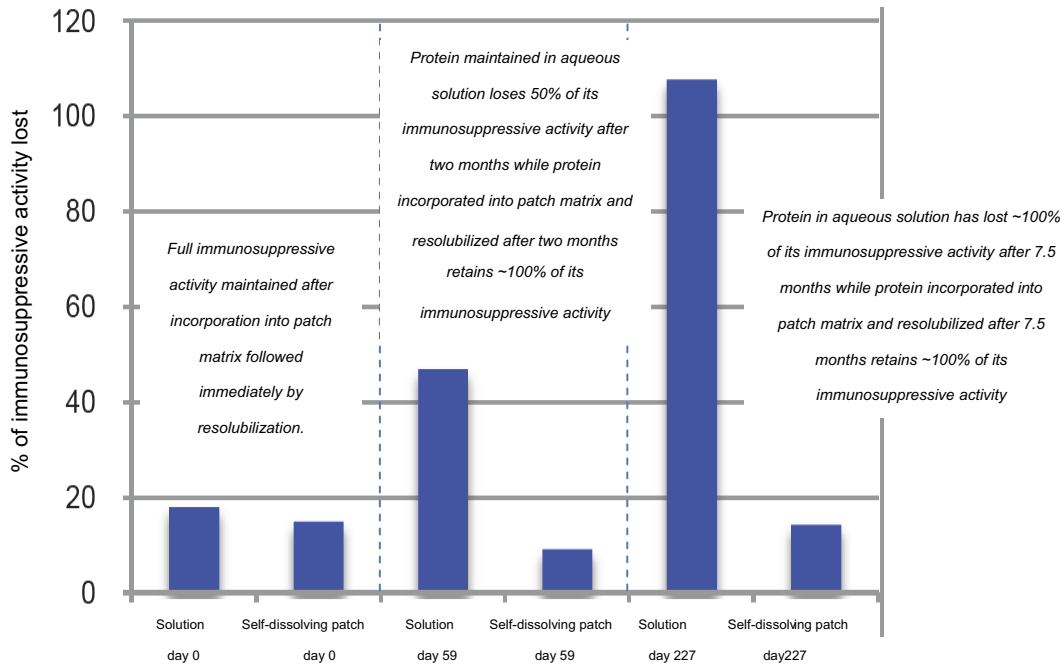

Figure 2 Suppression of cell inflammatory response by an 83,000-Dalton peptide maintained in aqueous solution or incorporated into the Self-Dissolving Patch. Full suppression of the inflammatory response by the protein is preserved in the matrix over an extended time, whereas no suppression is preserved over time in the aqueous solution of the protein.

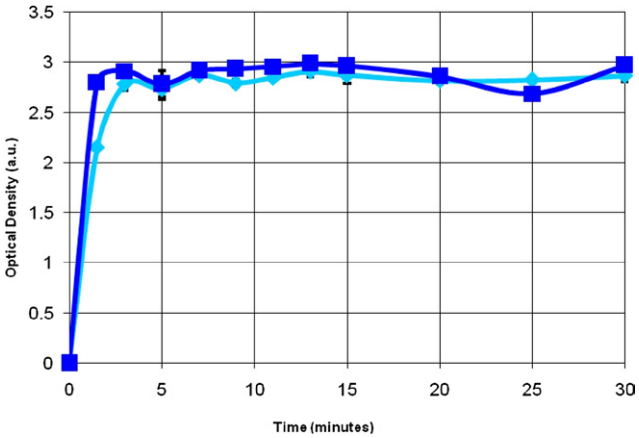

Figure 3 Dissolution of model active compound from Self-dissolving Patch: 100% of the active is released onto the skin with 2-3 minutes of the application.

Fibrous Matrices (eg, Cosmetic Patches)

In these systems the active ingredient is entrapped in a dissolved or dispersed state in large polymeric molecules typically arranged as nonwoven mats.[17] A wide range of large polymeric substances varying in polarity from hydrophilic to hydrophobic ends of the spectrum can be used for this purpose.[18] A major advantage of these matrices is that they possess adhesive properties, the strength of which depends on the choice of polymer. Additional advantages of these systems are their capacity to stabilize the active ingredient, ability to control the release of the active ingredient to the surface of the skin and ease of application. The biggest limitation of these systems may be the harsh processing conditions,[19] limited loading and delayed release of the active ingredient from the matrix. The most widely used applications of this system are in cosmetic patches intended primarily for controlled release of active ingredients over a duration of 4 hours to a day.

New-Generation Hybrid Delivery Systems

In addition to the 4 major types of skin delivery technologies described, there is a need for hybrid delivery systems that effectively protect active compounds in a matrix until the matrix is rapidly disrupted to release its payload directly onto the skin surface. In the emerging field of nanostructured materials (Fig. 1), structural manipulations at an atomic and molecular length scale are an essential pathway permitting the design of such innovative hybrids. The engineering of these nanostructured materials is a fascinating interdisciplinary area that brings together biology, material science, and nanotechnology. Depending on the desired structures and the exploitation of their unique properties that emerge at the nanometer scale, there are several approaches to engineering chemistries and compositions for skin delivery applications. The extraordinary versatility of the nanostructured materials is likely to enable some of the most innovative cosmeceutical formulations of unprecedented efficacy and functionality.

Advanced cosmeceutical products and treatments may require that bioactive components remain isolated until they are combined in situ on the skin surface at the time of application. Only a very sophisticated delivery system would allow for the individual components of the formulation to remain isolated until they combine and react at the time of application to produce the desired effect. An innovative hybrid delivery system that meets described storage and delivery requirements is the Self-Dissolving Patch (Agigma, Inc, Bridgewater, NJ). The Self-Dissolving Patch is a 3-dimensional matrix of nanofibers that is disrupted upon application onto the skin. Unlike most traditional formulations (eg, cream-base products, cotton or biocellulose skin patches), the Self-Dissolving Patch is compatible with a range of payloads composed of aqueous hydrophilic materials, oils, and lipophilic materials. The unique structure and composition of this system effectively protects the functional characteristics of even the most challenging actives, such as large proteins (Fig. 2) and enhances their delivery into the deeper layers of the skin (Fig. 3).

Polymeric matrices such as the Self-Dissolving Patch are also an ideal delivery system for low-molecular-weight molecules prone to degradation in aqueous solutions, such as vitamin C. Topical vitamin C products have a tendency to undergo rapid oxidation. A number of vitamin C esters and other derivatives have been developed as the stable forms of vitamin C, but their clinical effectiveness relative to L-ascorbic acid remains in doubt. The Self-Dissolving Patch system is engineered to preserve the functional characteristics of L-ascorbic acid using an innovative phase change mechanism: L-ascorbic acid molecules are stabilized within the polymeric matrix until the system is caused to change phase at the time of application and to release its payload onto the skin. Unique advantages of payload delivery

Table 1 Self-Dissolving Patch Delivery Compared with Creams and Conventional Skin Patches

	Cream Base	Conventional Patch	Self-Dissolving Patch
Loading capacity	5%-25%	5%-10%	Up to 80%
Delivery to skin	100%	20%-40%	100%
Controlled delivery	No	Yes	Yes
User-friendly	Yes	No	Yes
Compatibility with large number of drugs	Low	Low	High
Ability to deliver large molecules	Low	Low	High

by Self-dissolving Patch formulations are compared to several traditional delivery systems (Table 1).

Conclusions

In the last decade, a great amount of new information has become available on both the structure and function of the skin.[20] Today we understand that the skin is a very dynamic organ that is constantly renewing itself, and metabolically active as it interacts with the rest of the body. Much of the new information is based on the discoveries in molecular biology, which support new theories of aging and influence the trends in new skin care products and treatments. Medicinal approaches to delaying or modifying various mechanisms of aging are gaining popularity, whereas nanotechnology and innovative formulations are being implemented to support the development of more sophisticated cosmeceuticals. In addition to "older" nanotechnologies, such as nanoparticles and various fibrous matrices, there are nanoscale "hybrids" in development today, which promise to dramatically change the way we care for the skin. These hybrids are engineered to enable manipulation of the active ingredients individually while delivering them to skin in a controlled release fashion, to achieve the most effective outcome of the treatment.

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