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Microencapsulation
& Liquid Crystals



Skin Care Delivery Systems

Current trends for delivering
actives to the skin.

By Vispi Kanga
Cosmet-Pharm Consultants, LLC
Cresskill, NJ

Yves Saint Laurent's new Lisse Expert Advanced is billed as the first anti-wrinkle product that adapts to the morphology of each face to counteract the appearance of wrinkles.

The U.S. market for drug delivery technologies is expected to increase from \$19 billion in 2000 to more than \$41 billion by 2007.¹ Technological advances utilizing drug discovery approaches such as high-throughput screening, animal model systems, nanotechnology and biochemical assays have helped create a new generation of scientifically advanced skin care and cosmetic products. Although these new products do not make drug claims, they rely on many of the same techniques to deliver ingredients.

At the same time, advances in delivery technology have created new opportunities in the formulation of cosmeceuticals. They can now be administered through many routes by a variety of delivery systems.

Delivery systems not only play an increasingly important role in the development of effective skin care products but the technology continues to become more sophisticated and complex. It is important to obtain a better understanding of the influence of the biological environment on the release performance of various delivery systems. More than 90% of drugs approved since 1995 have poor solubility, poor permeability, or both. More than 40% of newly discovered drug entities have little or no water solubility.²

Many of these active agents are either peptides or proteins, yet skin is an extremely effective

barrier that is highly impermeable to large molecular weight peptides and proteins. Drugs with a high lipid solubility pass easily through the membrane. Drugs with low lipid solubility due to ionization need an active transport system since ionized molecules do not penetrate membranes. Lipid water distribution coefficient is more critical than lipid solubility alone for absorption.³

Drugs with a high lipid solubility pass easily through the membrane. In contrast, drugs with low lipid solubility will need a membrane carrier or active transport system. The formulation and delivery of these molecules in the skin is challenging. The partition coefficient of a drug depends upon both polarity and size. Drugs with high dipole moment, even though unionized, have low lipid solubility and, hence, penetrate poorly. Ionization not only reduces lipid solubility but also slows movement through charged membranes. Therefore, ionized molecules do not penetrate membranes. In such cases, membrane carriers that neutralize the charge or shield the molecule are required for absorption.



Estée Lauder's Hydra Complete Multi-Level moisture eye gel creme is said to continuously deliver moisture to the skin.

Small molecular weight peptides have the potential for enhancing targeting of compounds, and they may also have therapeutic effects by themselves. Peptides are used in products marketed by biopharmaceutical companies for their role in wound healing but their efficacy in improving the appearance of photo-damaged skin has only recently been determined.

Olay Regenerist anti-aging moisturizer line includes P&G's latest anti-aging technology in an exclusive amino-peptide complex, proven to regenerate cells in the stratum corneum so that they behave more like new skin. The limiting step for successful molecular targeting is the development of efficient peptide delivery systems. More than 70 companies have developed advanced drug delivery technologies for poorly water-soluble drugs.⁴

These approaches include solid dispersions, microemulsions, self-emulsifying systems, complexation, liposomes and the creation of nanostructured particles through particle size reduction and particle formation techniques. The application of molecular modeling, high-throughput cellular screening technologies and combinatorial chemistry has resulted in drug compounds with properties and activities more closely resembling the natural mediators in the body, which they are designed to mimic in their action.² A delivery system is designed to deliver the most efficacious amount of actives over a time period in a format that is consumer-friendly. For centuries, topical products such as lotions, creams and gels have been used to treat local skin disorders. The idea of using the skin as a route for systemic drug delivery, however, is fairly recent.

Novel Structures

Polymer skin delivery system designs provide considerable flexibility for formulators. Many of the polymers employed in these systems have bio and chemical compatibility with the drug and other components of the system such as penetration enhancers and pressure-sensitive adhesives. They provide consistent, effective delivery of a drug throughout the product's intended shelf life or delivery period and have generally-recognized-as-safe status.

In polymeric systems used for transdermal delivery, the drug reservoir or polymer matrix is sandwiched between two polymeric layers: an outer impervious backing layer

that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive and/or rate-controlling membrane.

Dendrimers or fractal polymers, a new class of monodispersed macromolecules developed during the past decade, provide the key to manufacturing of functional nanoscale materials that would have unique properties (chemical, biological, optical) that could be the basis of new nanoscale technology and devices. They have a highly branched, tree-like three-dimensional structure compared to conventional polymers, which are linear or long chains. Dendrimers consist of a series of chemical shells built around a small core molecule and feature four main components: a central or core unit, arms of identical size, linking or branched points and end functional groups. They are grown around a core and cross-linked to fix the structure. The terminal groups may be chemically different from the interior. The core can be removed to create a cavity.

The cavities are used as binding sites for small guest molecules that can be released in a slow equilibrium, making dendrimers promising slow delivery agents for perfumes and herbicides. When compared to their linear isomers, dendrimers are more soluble in common solvents that are not effective solvents for the linear isomer. In the pharmaceutical industry, fractal polymers are used to deliver drugs, chemical markers or genetic material right into cells or binding active particles to create an immune response. They are also used to create nanocapsules since dendrimers are amphiphilic and can self-organize into nanoscale structures.

Dendrimers have applications in skin treatments, hair care, bath and shower products and fragrances. The surface activity of dendrimer branches arises from the hydrophobic edge parts, and the hydrophilic core, so that these branches tend to stand up on a water surface like a nano-forest, cores (roots) going into the water, and the branches going up into the air. If a small amount of these dendrimers is spread, they form an extremely thin molecular film, only one molecule thick (a monolayer). A small addition of fractal polymer FPEC (fractal poly-epsilon caprolactam), increases the efficiency of cleaning agents.^{5,6}

Alternative Systems

Microspheres, microcapsules, nanoparticles, liposomes and microemulsions employ a variety of rate-controlling mechanisms, including matrix diffusion, membrane diffusion, biodegradation and osmosis. Microspheres and microcapsules differ from liposomal delivery systems in that they do not have an aqueous core but a solid polymer matrix or membrane. These particulate carrier systems are obtained by controlled precipitation of polymers, chemical cross-linking of soluble polymers, and interfacial polymerization of two monomers or high-pressure homogenization technique. The drug is gradually released by erosion or diffusion from the particles. Depot formulations of short acting peptides have been successfully developed using micro particle technology.

Sonke Svenson and Christopher Tucker of Dow Chemical produce crystalline nanoparticles by preparing a stable o/w emulsion, loading the emulsion with a drug solution, and then removing the solvents to give redispersible drug nanoparticles. It is fast, easily scalable, requires only small amounts of stabilizers and is less stressful to the drug because the emulsion is prepared in its absence, and avoids the risk of contaminating the samples with solid impurities.

Amorphous nanoparticles of poorly water-soluble drugs have been developed via novel processes for enhanced dissolution rates and improving solubility and bioavailability. The processes involve rapid expansion from supercritical to aqueous solution (RESAS) and evaporative precipitation into aqueous solution (EPAS). In both processes, the ability to trap drug particles in an amorphous state results from rapid phase separation and stabilization of the resulting particles with polymers and surfactants. This is produced by evaporative precipitation into aqueous solution containing a surfactant stabilizer. Aqueous suspensions formed by EPAS were centrifuged to remove the

nonadsorbed surfactant. The resulting surfactant-coated drug particles had extremely high drug-to-surfactant ratios greater than five, corresponding to potencies as high as 93%. Drug levels as high as 37.9 mg/ml of 400-700 nm particles were achieved in a 5.0% surfactant solution.⁷

Microgels are nanosized crosslinked particles synthesized by inverse microemulsion polymerization. They have very narrow size distributions and can form stable suspensions in water. The particle size of microgels decreases as the crosslinking density increases. Due to their open network-type structure, microgels have large surface areas and are used as carriers for delivering drugs. Microgels may be modified by attaching hydrophobic groups; negatively charged microgels have carboxylic acid groups into their backbone.

Nanogels are crosslinked, sub-micrometer sized particles made of hydrophilic polymers. They are soluble in water, but have properties different from linear macromolecules of similar molecular weight. Researchers at Columbia University, New York have synthesized polyacrylamide nanogels comprised of nanosized cross-linked particles with very narrow particle size distribution (50nm) and vast amounts of interstitial space. Active encapsulation experiments showed that polyacrylamide nanogels are hydrophobic, highly binding, dependent on the degree of cross-linking density and effective in time-release applications.⁸

Penetration Enhancers

The skin itself is a rather complex, heterogeneous membrane and its penetration pathways and skin lipid-structure are not well understood. Many delivery systems rely on penetration enhancers to increase drug transport through the skin. Researchers must develop a better understanding of the functioning of penetration enhancers in the stratum corneum lipid structure and in the drug penetration pathway.

Skin patches hold promise for transcutaneous and transdermal administration of a broad scope of skin treatments. Success depends on a variety of biological, physiological, biochemical and biophysical factors including the thickness, composition and integrity of the stratum corneum; size and structure of the molecule (such as molecular weight); state of skin hydration; degree of partitioning of the drug and associated components into the skin; lipid solubility; depot (reservoir) of drug in skin and physicochemical properties of the drug. Patches can irritate the skin, since they deliver drug through the skin by being occlusive. In the cosmetics industry, vitamin C patches are promoted to improve facial-line appearance and to de-emphasize wrinkles. Other ingredients such as sea kelp are also delivered through the skin.

External Effects Can Enhance Delivery

Phonophoresis is the application of ultrasound to the skin to increase the permeability of the membrane and allow drugs to be administered with greater effectiveness. Ultrasound enhancement does not cause permanent damage to the skin's protective properties or to underlying muscle tissues. Frequency range of 1-3 MHz increases drug permeability moderately and only a short distance into the skin. Frequency range of 20-100 kHz is effective for large molecules. It increases drug transport across the skin by cavitation mechanism. The thermal effect of phonophoresis increases the kinetic energy of both the drug molecules and the proteins, lipids and carbohydrates in the cell membrane.

Phonophoresis requires the use of an ultrasonic coupling medium, which facilitates an efficient transfer of energy between the transducer and the skin surface. The medium may be either a balanced viscous gel or an aqueous solution. Other cosmetic products may be homogeneously dispersed within the complying medium or deposited directly on the skin and the overlying complying gel subsequently added. It is important to stress that formulation design of the donor vehicle/complying agent may radically affect the cosmetic efficacy in these systems.⁹

Thus the drug delivery is via an appropriate carrier such as lotion, aqueous gel,

ointment or suspension that preferably has an absorption coefficient similar to water. Phonophoresis is a great tool to facilitate the absorption of oils, fat soluble vitamins, liposome products, emulsions and water soluble agents. In pharmaceuticals, it is currently used for transcutaneous delivery of NSAIDs, antibiotics for fungal infections, hydrocortisone and anesthetics.

Iontophoresis has the potential to deliver macromolecules across the skin, and companies such as IoMed and Becton Dickinson are investing effort into formulating drugs for administration by this methodology. It is a delivery system that delivers drug ions through the skin using an electric current and is based on the principle that "like charges" repel "like charges" so the drug ions are repelled or pushed into the underlying tissue. It is a localized, non-invasive, effective and rapid method of delivering water soluble, ionized medication into the skin. An iontophoresis patch consists of two electrodes.

The printable conductive ink is one of the most commonly used technologies in iontophoresis electrode design. One or both electrodes are made of Ag/AgCl printable conductive ink coating, covered by a layer of hydrogel containing the drug and a liner. The patch is powered by a thin 1 x 1 inch battery made by printing conductive inks.¹⁰ The active ingredient or drug must be water soluble, ionic and with a molecular weight below <5000. Research shows that the drug delivery effectiveness can be increased by a third through iontophoresis.

This technology has further advanced because of Power Paper's thin, flexible, easy to use, disposable power source incorporated into a cosmetic patch. The company's core technology is the use of proprietary ultra-thin micro electronic components that are integrated into a simple cosmetic patch. Power Paper works exactly like a traditional battery but is nearly as thin as a piece of paper. A Power Paper cell is 0.5mm thick and can generate 1.5 volts of electricity. A zinc and manganese dioxide-based cathode and anode are fabricated from proprietary inks coatings. Silkscreen printing presses are used to print the batteries onto paper and other substrates. Bulk cost of these batteries is only one cent/sq.inch, with a shelf life greater than three years.

PowerCosmetics offers two product lines of skin care: Cosmetic enhancers for anti-aging, skin lightening, cellulite treatment and moisturization; and cosmetic vitalizer patches to fit facial/body contours for skin rejuvenation.

Needle-Free Injection Devices

Perhaps the most exciting technological advance in drug delivery systems is the use of needle-free injection devices for "firing" molecules through the skin at high velocity. Several companies are competing with different devices and interest in these products is high judging by the high profile collaborators involved.

In their quest to solve skin problems associated with an aging population, marketers are creating products that incorporate an array of effective, active materials. To ensure that these materials reach their intended targets, more marketers and their suppliers are devoting a greater portion of their research efforts to develop effective skin care delivery systems.

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