Liposomes

Their role in personal care products, cosmetics

Are liposomes a marketing gimmick or a revolutionary way to offer functionality in cosmetic and personal care products?

"In cosmetics, a part of what you're selling is promise. Liposomes sound sexy. By promoting products as containing liposomes, cosmetic manufacturers are selling a promise of more effective delivery and greater efficacy," according to Thomas Spencer, vice-president of research and development of Cygnus Therapeutics and a past president of the International Society for Bioengineering and The Skin.

What is being promised, however, is something that still is debated within the cosmetic industry. Researchers have shown that liposomes themselves, when applied topically, probably do not penetrate below the stratum corneum (horny layer) of the skin. However, there are indications they may increase moisture in the top layers of the skin and deliver active ingredients to these layers.

What are liposomes?
Liposomes are microscopic spheres made from a variety of fatty materials, primarily phospholipids. Their similarity to cell membranes and their ability to carry substances have led manufacturers to promote them as a means to protect active ingredients in products and to provide time-release properties.

Liposomes are made of molecules with hydrophilic and hydrophobic ends that arrange themselves to form sub-microscopic hollow spheres. The outside of liposomes consist of multiple lipid layers; their interior can retain water or water-soluble actives. They can encapsulate both water- and oil-soluble ingredients. Liposomes can be made up of one or more concentric lipid bilayers and can range in size from a nanometer to several micrometers in diameter.

"An easy way to describe liposomes is to think of them as empty cells in which you can program the contents," according to Geoffrey J. Brooks of Brooks Industries Inc. and Robert C. McManus of Chemmark Development Inc. in an October 1990 article in INFORM.

"While phospholipids are natural components of cell membranes, the material actually used in cosmetics may be obtained either from natural or synthetic sources. When properly mixed with water, phospholipids form liposome spheres, which can "trap" any substance that will dissolve in water or oil," according to an article entitled "Cosmetic Ingredients: Understanding the Puffery" published in the May 1992 issue of FDA Consumer.
Lecithin, a natural phospholipid which consists primarily of phosphatidylcholine, is a building block for many liposomes. Liposomes containing a high proportion of phosphatidylcholine have been shown to increase skin hydration, according to J. Röding and M. Ghyczy in an article published in *Seifen-Öle-Fette-Wachse (SÖFW)* in 1991.

Although phospholipids commonly are used, they can be very expensive because of extraction and purification costs. Some companies have chosen to use such source materials as nonionic surfactants. L’Oréal of France, for instance, has patented nonionic surfactant vesicles (NSV) that were developed for stability reasons.

In an article in the August 1991 issue of *Cosmetics & Toiletries*, Hans E. Junginger and colleagues from Leiden University, The Netherlands, explained that NSV are prepared from such nonionic surfactants as polyoxymethylene alkylether, polyoxymethylene alkylerster and saccharose diester. NSV are similar in structure to phospholipid-based liposomes; both can be stabilized by cholesterol.

Meanwhile, Micro Vesicular Systems Inc. (MVS), whose parent company is IGI, uses a variety of low-cost materials normally utilized in developing cosmetics to produce liposomal-type structures for cosmetic and toiletry applications.

**How do they work?**

Although liposomes themselves do not go through the horny layer of the skin, researchers have found that components may do so.

“The chance of a whole liposome going through the stratum corneum is like a basketball going through a chain-link fence,” according to Norman Weiner of the College of Pharmacy, University of Michigan at Ann Arbor. However, there may be a chance that liposomes can enter through hair follicles. “That question still must be resolved,” he said.

Junginger and colleagues noted that skin lipids strongly differ from the chemical structures of phospholipids in liposomes and the nonionic surfactants in NSV. “The probability that liposomes and niosomes (an NSV)
may be able to diffuse as intact vesicular structures along the intercellular route is relatively small," they wrote, adding, "It may be possible for small unilamellar liposomes or niosomes to enter the skin along hair shafts or sweat ducts although the proportion of intact vesicular structures that may reach the dermis will be negligible."

They also reported that components of liposomes and NSV—particularly phosphatidylcholine—may interact as dispersed molecules with the skin lipids and provide some beneficial effects in cosmetics. "They may be able to replenish a lipid deficiency in the skin by incorporating phospholipids or suitable nonionic surfactant and simultaneously reduce the transepidermal water loss (TEWL) by increasing the liquid-crystalline state of the skin lipids," they concluded.

This also is the view of Franklin J. Wright of Lancôme. "The lipids introduced in the stratum corneum via NSV are physically arranged the way skin lipids are naturally organized. With NSV, not only do we mimic the chemistry of these lipids but also their physics." In his article, Williams described the pro-liposome approach—a new method used in the Lucas Meyer's Pro-Lipo program—in which water is added to a carefully chosen mixture of phospholipids in a hydrophilic medium to cause the spontaneous formation of liposomes (see illustration, page 1173). "One of the major disadvantages of most methods of liposome preparation is that it is often difficult, in some cases impossible, to load the liposomes with active ingredients. The pro-liposome approach has the major advantage that the liposomes can readily be loaded with hydrophilic or hydrophobic ingredients," according to Williams, noting that the active ingredient is added into the bilayer system prior to final liposome formation.

Lucas Meyer, which also markets lecithins to liposome manufacturers, sells its patented Pro-Lipo formulations to cosmetic and personal care companies which then blend in desired active ingredients. "These are really the lipid liposome precursor," according to Roger Sinram, technical director at Lucas Meyer Inc. in Decatur, Illinois.

Sinram said the pro-liposomes can provide higher loading levels of active ingredients than traditional liposomes and are more economical. Lucas Meyer launched the Pro-Lipo system in Europe a year ago and in the United States in May. The Pro-Lipo formulations are converted into stable liposomes only after extra water is added in a two-step dilution regimen. After the first stage, a concentrated liposome suspension forms. Subsequent addition of water simply reduces the liposome concentration without affecting the contents trapped in the liposomes.

The main hurdles to wider exploitation of liposomes have been cost and processing difficulties, according to John M. Behan, director of applied research for Quest International, for one, has patents covering liposome systems for carrying perfume and similar materials and for the use of such systems in detergent and emulsion products. These are based on nonphospholipid surfactants optionally structured by perfume ingredients. These systems can be manufactured using simple low-shear mixing, avoiding complex high shear and solvent methods used for phospholipid liposomes, Behan said. "Traditional liposomes are usually submicron in size while the Quest systems are designed to be one to ten microns. This size give an advantage in loading capacity," he added.

Meanwhile, R.A. Brunke and E. Charlet of Düsseldorf, Germany, in a Sept. 1, 1991, article in SÖFW, noted that the Kavitator technology devel-
opened by the New Standard Company in Düsseldorf, Germany, is able to produce liposome vesicles inexpensively. The Kavitator is a small production unit, in which two reaction streams are directed toward each other under high pressure. At the reaction center, cavitation forces and collision forces break large particles into small ones.

**Product applications**

Touted as nontoxic and biodegradable, liposomes can increase the value of cosmetic products by encapsulating a variety of ingredients such as moisturizers, skin care agents, sunscreens, vitamins and tanning agents in moisturizing creams, cleansing creams, aftershave lotions, hair products and bath lotions.

In a 1990 article published in *Advanced Drug Deliver Reviews*, Weiner and Egbaria noted increasing interest in the use of liposomes in skin gels and skin creams. "Vegetable phospholipids are widely used for topical applications in cosmetics and dermatology, since they have a high content of esterified essential fatty acids, especially linoleic acid which is believed to increase the barrier function of the skin and decrease water loss within a short period of time after application. Soya phospholipids or other vegetable phospholipids, due to their surface activity and their ability to form liposomes, are also an ideal source for possible transport of linoleic acid into the skin."

In Europe, nearly all of the major cosmetic companies—L'Oréal, Lancôme, Christian Dior, Payot, Lancaster, Beiersdorf and Avon—market products containing liposomes. Unilever, L'Oréal and Christian Dior are among the companies with patents related to liposome applications and technology.

In the United States, such companies as Avon, Elizabeth Arden, Chesebrough-Pond's, Estée Lauder, Revlon and Shaklee have products containing liposomes, and European companies such as L'Oréal, Lancôme and Beiersdorf have introduced their products here as well. Companies in the Far East also market cosmetics containing liposomes.

Manufacturers claim liposomes can provide an elegant feel on the skin and preferential delivery of moisturizers to dry or damaged parts of the skin. Cosmetic manufacturers add other skin care agents to liposomes to achieve a particular cosmetic effect or to create a product with unique attributes. Liposomes can be used to encapsulate cosmetic ingredients and release them over time.

"I personally believe that products using liposomes show advantages over regular emulsions," according to Brooks, who is chief technical officer for Brooks Industries. "When these products are used, the skin appears to be in better shape and the moisturizing effect seems to last longer. If you add liposomes to a good formula, they will make it better. People really like the way these products feel on the skin."

Avon Products, which has used liposomes since the early 1990s mostly in skin care products, sees them as a way to protect a particular active ingredient in the product.

"Consumers like the delivery form," according to Janice Teal, director of research and development for Avon Skin Care Laboratories. Teal noted that liposomes thus far are used more widely in Europe than in the United States. Because liposomes are "a high-tech concept," consumers probably do not understand how they work but rather notice how skin care products containing liposomes make their skin feel, she added.

Avon has its liposomes custom-made to include such actives as vitamins A, C, E and β-carotene. Another liposome in its Moisture Therapy line contains allantoin as the active ingredient, Teal said. Avon also has two gels containing liposomes in its Visible Improvement Program line for use around the eyes and on the face.

Lancôme, which has marketed its Niosôme Daytime Age Treatment skin cream since 1987, in September introduced an improved product, Niosôme + Perfected Age Treatment. "The increased understanding of the nature and organization of the intercellular lipids in the *stratum corneum* which has resulted from the basic research carried out in the last 10 to 15 years has allowed Lancôme to produce more efficient, as well as more cosmetically elegant, NSV such as those included in Niosôme +," according to Wright, who added, "The new NSV even more closely resemble skin lipids, and their increased stability permits the delivery of a more powerful array of actives."

Lancôme's first NSV used single-chain nonionic saturated lipids; its latest version uses new nonionic lipids composed of 1-, 2- and 3-chain molecules. The Niosôme + formula also includes an anti-free radical radical complex composed of lactoferrine, luctoperoxidase, guanosine and glycerol.

Recently joining the list of U.S. companies to market products using liposomes, Chesebrough-Pond's USA, part of the Unilever Personal Care Group, has reformulated its Vaseline Intensive Care Hand & Nail Formula to contain liposomes. The new formulation is a hand and body lotion in which liposome technology provides targeted delivery of a patented moisturizing humectant ingredient, according to Dipak Ghosh, manager of product development for skin care at Chesebrough-Pond's.

Revlon, meanwhile, uses liposomes in skin lotions, sun protection products, gels and creams for use around the eyes, body lotions and decorative cosmetics such as make-up and lipstick. Other products containing liposomes in the U.S. market include Beiersdorf's Nivea line, L'Oréal's Plenitude line, and Parfums Christian Dior's "Capture" line of moisture creams and protectants. As previously mentioned, companies such as Quest International have developed liposomes to entrap perfumes and fragrances to prolong their effect in cosmetics and other products.

**Liposome suppliers**

Some of the major players in the cosmetic industry—Unilever, L'Oréal,
Christian Dior and Revlon—have their own trademarked cosmetic liposomes. Others such as Avon use outside suppliers.

Brooks Industries of South Plainfield, New Jersey, markets liposomes produced by sister company Chemmark Development Inc., also of South Plainfield. Microfluidics Corp. of Newton, Massachusetts, is another company that supplies liposomes for cosmetics and personal care uses. Both Brooks and Microfluidics use phospholipids as the source material.

Microfluidics uses patented technology to produce its Dermasome brand of cosmetic liposomes. This high-pressure method produces uniform, submicron-size liposomes that are unilamellar in structure.

"Unilamellar liposomes are more economical than those that are multilamellar because they allow the use of less of the expensive ingredient—the active," according to Carol Ostrum, marketing manager for Microfluidics. "Some of our typically encapsulated actives include β-carotene, skin respiratory factor, and vitamins A, C and E."

Because very pure phospholipid fractions from lecithin can be very expensive, Brooks said his company has sought ways of using less expensive raw materials.

Meanwhile, IGI, through its subsidiary MVS, has become the only U.S. liposome supplier of exclusively nonphospholipid-based liposomes, according to Denis O'Donnell, vice-president of medical affairs for MVS. Although originally targeting applications in poultry vaccines, IGI now is marketing these for cosmetics, personal care products, pharmaceuticals, pesticides, coatings and paints. In fact in September, IGI announced it will produce its lipid vesicle products under the trademark Novasome for three U.S. cosmetic and personal care companies for skin care applications.

IGI commercially produces Novasomes at its Buena, New Jersey, facility, where it can produce more than 5,000 pounds a day. The patented Novamix process uses rapid-flow mixing to convert a wide variety of materials normally used in emulsion technology for cosmetics and toiletries development into liposomal-type structures, according to Stephen Hoch, IGI's vice-president of marketing.

Not only do these materials cost less than phospholipids, but they also have a higher load capacity for active ingredients, Hoch said. Also, these structures are very stable, with tests showing that they remain intact in finished products. A product brochure on Novasome technology notes that Novasome vesicles are much smaller than ordinary microcapsules and have deformable, rather than rigid, walls.

In Canada, Canamino Inc., a joint venture of Nuvotech Ventures International and Philom Bios, has been formed to commercialize technologies and to market products specifically developed for the cosmetic and personal care industry by the National Research Council of Canada, POS Pilot Plant Corporation and Philom Bios. "Our mission is to market products from plant materials to the cosmetics industry," according to John Schaw of Canamino. POS has provided methods for producing the phospholipids used in making liposomes. In addition to POS, Canamino is working with the University of Saskatchewan. Canamino also has the technology to encapsulate vitamin E.

"Our intent is to have liposome products to offer," he said, adding, "We're at the early stages of product development." Some of the ingredients Canamino might encapsulate in liposomes are borage oil, β-glucan from oats and vitamin E.

Meanwhile, The Liposome Co. Inc. in Princeton, New Jersey, has chosen to focus on injectable pharmaceutical applications in the areas of cancer, life-threatening infections and cardiovascular disease rather than cosmetic and personal care uses. "We have looked at topical applications of liposomes, but these were for prescription products, primarily in the areas of ophthalmics and anti-fungals," according to Anne M. Van Lent, senior vice-president for The Liposome Co.

Van Lent cautioned that cosmetic and personal care manufacturers must be careful in crafting advertising claims for products containing liposomes with encapsulated active ingredients. "If the companies make therapeutic claims for their products, they will have to prove them to the satisfaction of the U.S. Food and Drug Administration (FDA). Also, there is a very fine line for products claiming deep intradermal penetration and then proving that there is no transdermal movement of active ingredients into the bloodstream," she said.

Weiner agreed: "If the liposomes do actually help bring materials down into the skin, one has to look at whether this is then a cosmetic or a drug. It's a line I don't think the cosmetic industry wants to cross. Otherwise, it becomes an issue for FDA."
**FEATURE**

**Formulation challenges**

Although methods for forming liposomes have improved during the past several years, some believe further developments are needed. “Full-scale production of liposomes requires inexpensive materials, reproducible methods of generating liposomes in large quantities, high trapping efficiencies, high active ingredient lipid ratio and long shelf life,” Marta Juszynski and colleagues at the Soreq Nuclear Research Center in Israel wrote in a 1991 article in SÖFW.

“Entrapment efficiency and stability are two main factors which have to be considered when practical uses of loaded liposomes are concerned. Evidence accumulated over the past two years shows that the yield can vary from one type of liposomes to the other, and is highly dependent on the physicochemical characteristics of the lipids and of the encapsulated compound,” they wrote.

In liposomal formulations, care must be taken to avoid using surfactants and materials that can act as a cosolvent for the phospholipid or break down the bilayers. Liposomes may be adversely affected by some preservatives and perfumes and are subject to oxidation.

Creams containing traditional phospholipid-based liposomes are relatively difficult to formulate because the emulsion may separate or the liposome may break down when in contact with the oil phase of the emulsion. “Phospholipid-based liposomes do well in gel systems but not in emulsion systems,” according to George A. Fiore, president of Revlon Research Center in Edison, New Jersey.

In fact, stability is one of the limitations of using phospholipid-based liposomes in cosmetics and personal care products. “Liposomes can be compatible with creams and lotions. Sometimes they break down and sometimes they don’t,” Weiner said. Noting that a product such as Christian Dior’s Capture has successfully incorporated liposomes in an emulsion system, Weiner warned, however, that liposomes will break down in the wrong formulation.

“Because phospholipid-based liposomes don’t hold up particularly in certain formulations, they can disintegrate in the product on the shelf and thus may not be intact at the time the consumer purchases the product,” Fiore said. “The chemist has to make a product suitable for the liposome, rather than a product well suited for the consumer’s needs.”

A third stumbling block is cost. “Traditional phospholipid liposomes are incredibly expensive,” Fiore said. O’Donnell of MVS agreed. “The raw materials for phospholipid liposomes can run to $25,000 or more per kilogram. They require organic solvents in their manufacture and they are inherently unstable. They also are difficult to produce on a large scale.”

In contrast, the emulsion-type materials used by MVS to produce its Novasomes cost between $5 and $10 a kilogram and do not require organic solvents in the manufacturing process, O’Donnell said, noting that MVS has Novasomes that are still stable after five years on the shelf.

Both Weiner and Fiore predicted increased use of nonphospholipid-based materials in liposomes. “There is a growing trend toward synthetic materials,” Weiner said. Nonphospholipid-type liposomes are relatively inexpensive and are used by such companies as L’Oréal and Revlon. “From our perspective, they perform as well or better and are more stable than the traditional liposomes,” Fiore said. They also are more durable than phospholipid-based liposomes. “You can put them into a hostile environment in a product and they will last two years or more, versus six months for the traditional liposomes,” he explained.

However, companies such as Revlon also have gone to another improved form of carrier vehicle which is not liposome-based: polymeric capsules. These, Fiore said, deliver an ingredient such as a moisturizing agent to a site when enzymes on the skin break down the tiny capsules.

“Polymeric forms are cheaper still, and we are able to pretty much design the polymeric shell to house whatever agent we want them to house. With liposomes, you can only put in ingredients that are compatible,” Fiore said. The polymeric capsules, for instance, have been used by Revlon to encapsulate both moisturizing and coloring agents in lipsticks. As the enzymes break down the capsules, moisturizing and color are provided over time.

“I believe you will see cosmetic and personal care companies walking away from traditional phospholipid-based liposomes,” Fiore said. “They just don’t hold up as well as other carriers.” However, he predicted, such traditional liposomes will see more demand in injectables and other pharmaceutical applications.

“Liposomes have a bright future prescription drugs or such applications as a cough syrup because they are a natural transportation system for the body and also because they can be used to target to a specific organ,” Fiore said, adding, “The truth is, they’re too difficult for us to use in the cosmetic industry, and really, they’re too good for us.”

This article highlighting the use of liposomes in cosmetics and personal care products was written by INFORM senior editor/writer Barbara Fitch Haumann.