Chirally Correct Skin Care… Or Is It?

by Sam Dhatt

While chirality is actually nothing new to science and the pharmaceutical drug industry, it is a relatively new concept to skin care. But what do chirally correct ingredients offer the skin and can they provide real benefits otherwise unmatched?

In 1847, renowned French chemist Louis Pasteur first discovered the concept of chirality as a graduate student while studying two acids in wine. He observed that while the chemical composition of tartrate and paratartrate were identical, their crystals polarized differently. This observation led him to understand that many molecules have two "mirror-image" parts – that is, they are the same in all ways physically and chemically with one exception: how these individual isomers, or single enantiomers, link together and react with other molecules in the body.

Chirality is often described as the "handedness" of molecules. The isomers are typically referenced by either an "L" or "D" notation designating the two parts. To illustrate, think of your left and right hand. They are mirror images of each other, but could you fit your left hand inside a right-handed glove? The same holds true for chiral isomers, which do not link perfectly with one another and are not superimposable but are, rather, mirror images of each other.

Lactic acid is an example of a common skin care ingredient with two isomeric chiral forms. If you were to split the lactic acid molecule down the middle, there would be no plane of symmetry.

Assymmetrical in their cross-sections, these isomers vary in their rotation, or linking mechanism, which can cause the single isomers to react differently with other molecules in the body. As a result, the consequences can be that while one enantiomer offers desirable functions, the other may have no effect, negate the value of the favored isomer, or actually do the body harm in some way.

Since Pasteur's discovery, many important ingestible drugs have been produced using "chirally correct" ingredients, optimizing the most effective and therapeutic single enantiomer while discarding the other less effective or harmful part of the molecular pair. By using chirally correct ingredients, pharmaceutical manufacturers can ensure that the more beneficial isomers will link up correctly with the receptors inside the body to produce a favored response.

Sometimes, the effect is critical to eliciting a therapeutic result and even necessary to avoiding disaster. In the 1950s, for example, many pregnant women taking the drug Thalidomide for "morning sickness" gave birth to babies with severe birth defects. It was later discovered that while the D-isomer curbed the morning sickness and did not harm the body, the L-isomer of the drug actually caused the devastating birth defects that resulted.

Today, pharmaceutical companies are making great inroads in discovering new applications and ways to harness the science. But do chirally correct ingredients have a place in skin care? Many skin care manufacturers tout their chirally correct ingredients as superior formulations that contain only

the beneficial isomers, which will ensure deep absorption into the skin and foster positive results with no allergic reactions.

While the claims may sound good, chirally correct may not be the most correct concept after all when applied to skin.

Breaking Down the Science

Jeannette Graf, M.D., F.A.A.D., a Great Neck, NY-based clinical and research dermatologist and recipient of the NIH Outstanding Achievement Award, has been watching chirally correct ingredients in skin care for years.

"While it sounds good in theory and chirality has been applied in oral medication, the bottom line is there's not one iota of science to support the premise of chirally correct ingredients in skin care products," she says. "I really want to see the science. I've looked and looked, and there's absolutely nothing to support enantiomer, chirally correct ingredients in skin care."

Chirally correct ingredients can have profound effects when ingested as drugs in the body, but they become a non-issue when applied to the skin for several reasons.

According to Dean Handley, Ph.D., MBA, JD, former executive director of medical communications at the pharmaceutical company Sepracor and one of the world's foremost authorities on chirality, "chirally correct ingredients are unproven and irrelevant in skin care." "Einstein once said, 'The thing that can't be measured can't be understood,' and that is the case here," Handley notes. "Chirally correct claims simply aren't based on any measurements."

By their very nature, plant- and animal-derived ingredients are chirally correct. Whereas, synthetics produced by chemists result in racemic forms (containing both isomers or single isomers), the enzymes in plant- and animal-derived sources produce molecules that are chirally correct naturally. Therefore, many of the natural ingredients used in skin care, including palmitic acid, fatty acids, emollients, vitamins, and aromatics, are inherently chirally correct, says Handley.

While some manufacturers market their chirally correct formulas as superior, the truth is many, if not most, skin care companies are already using chirally correct actives as a consequence of what is naturally being piped down the supply chain.

Consider vitamin C. Topical vitamin C offers many benefits to the skin. This prime antioxidant diminishes hyperpigmentation and even helps to stimulate collagen. L-ascorbic acid is able to perform all of these beneficial roles. D-ascorbic acid, on the other hand, leads to negative effects, such as dryness, irritation, and the production of free radicals. As a result, manufacturers of pure vitamin C products are already using the L-ascorbic acid form, which is more easily absorbed.

Furthermore, "most amino acids are L forms, while carbohydrates are D forms with a few exceptions," says Peter Pugliese, M.D., an anti-aging skin care authority and a pioneer of cosmetic research, formulation, and education who confers with Handley.

"The application of chiral products to cosmetic skin care is not warranted and appears to be a scare tactic," he notes.

"Even synthetic racemic ingredients do not *a priori* impose a negative consequence to the skin," Handley says, "because any unfavorable reaction would become immediately apparent." This was the case with Thalidomide and the drug Dopamine. In its L form, Dopamine is a nerve protectant, yet in its D form, it is a toxin that produces a profound negative mental state.

"When we make a mistake with a racemic, we usually know it right away," says Handley.

In skin care, manufacturers of chirally correct ingredients claim their formulations can avoid the allergic reactions, ineffectiveness, and penetration issues that sometimes arise with using non-chirally correct ingredients. Closer examination of the causes of these reactions, however, demonstrates that other factors are actually at play.

Pharmaceutically Correct; Cosmetically Questionable

Chirally correct ingredients hold a valid place in pharmaceuticals that are ingested in the body and used on a systemic level. These chirally uniform drugs typically work better than their racemate forms because the body has receptors that interact with the specific shapes of these chirally correct molecules, providing better linkage and thus a superior end result.

Until recently, synthetic drugs were only available in their racemate form. But as new advances in chiral technology arise, more single isomer drugs are expected to sweep the pharmaceutical industry.

Indeed, chiral chemistry is already big business. In 2005, single isomer therapies rang up sales of $225 billion, representing 37 percent of the total $602 billion final formulation pharmaceutical market, according to estimates from Technology Catalysts International, Falls Church, Va, and IMS Health, Plymouth Meeting, Pa. With an 11 percent annual growth, chirally correct drugs are now keeping pace with the rest of the pharmaceutical industry.

Two of the best examples are Pfizer's Lipitor, which logged $3.3 billion in sales in 2005, and Zoloft, the best-selling drug in the world with $12.8 billion in sales in 2007.

For the pharmaceutical industry, chirality helps many large drug companies avoid best-selling drugs from going generic. By tweaking the chemistry with chiral formulations, these pharmaceutical companies can use the amended formulation to extend rights to their intellectual property.

And there are therapeutic benefits for a wide application of chirally correct ingredients. In the agrochemical sector,

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chiral ingredients offer more eco-friendly insecticides. For the biochemical market, chirality offers efficient peptides and vitamins for dietary supplements and functional foods. For the fragrance industry, these single isomers deliver greater stability, biodegradable ingredients, and even more intense scents.

However, according to skin chemists and researchers, the skin is a different playing field. "The skin cannot identify certain types of isomers that easily," says Chim Potini, director of operations at Hale Cosmeceuticals, Bloomington, Ill. "They're just not that easy to recognize. And sometimes in a topical skin product, it's better to have a combination of all isomers in skin products."

Vitamin E's tocotrienol and tocopherol isomers, for example, offer a synergistic combination that adds up to greater antioxidant value than any one of its single isomers.

Furthermore, some molecules that are commonly used in cosmetic chemistry cannot be chirally correct because of their chemical constitution. For instance, retinoic acid (vitamin A) is not made up of chirally correct molecules with mirror-image isomers. Rather, retinoic acid is comprised of geometric isomers that have the same chemical formula and the same atoms in each molecule, but the geometry around the double bond is different and each may have different biological effects, says Michelle MacRae, a formulation chemist in research and development at Allure Cosmetics, Hayward, Calif. As a result, it is simply incorrect to call retinoic acid chirally correct. The concept simply does not apply.

Absorption: Function of Chirality or Other Factors?

Chirally correct proponents claim that their single enantiomer products ensure superior penetration and absorption. However, the true dynamics behind the absorbability and penetration ability of a formula is more of a function of its actives' molecular size and the delivery system, such as liposomes.

Polyolprepolymer 2 (PP-2), for example, is a topical delivery system that forms a non-invasive liquid reservoir on the upper layers of the skin to deposit significant amounts of skin care agents in the stratum corneum and epidermis.

An *in vitro* skin permeation study measuring the delivery of salicylic acid into human skin with and without PP-2 found a greater amount of salicylic acid stays on and in the upper layers of the skin in the presence of PP-2. Another *in vitro* study comparing the release of magnesium ascorbyl phosphate with and without PP-2 showed a significant increase in deposition with the PP-2 formula.

Layering technology, in which the lightest formulations (i.e. serums) are applied first, followed by more emollient, heavier-weighted formulations to maximize absorption also play a key role.

"Show me one ingredient that is chirally correct and has superior penetration versus the same non-chirally correct ingredient in an identical formulation. You can't! Penetration is more a function of the size of the molecule and the strength of the liposome or technology of the delivery systevm," says Graf.

Allergens or Just an Irritating Distraction?

Some advocates of chirally correct skin care claim that the linkage of the favored isomers in chiral formulas present less potential for dryness, irritation, and allergic reactions. Yet, these reactions may be more attributable to other factors, namely irritants in a product's formula base.

To say a non-chirally correct formula can cause an allergic reaction "makes zero sense," says Graf. "It's not usually the active ingredients that are responsible," she notes. "It's usually the skin being sensitized to a preservative or some ingredient that creates an irritation, which is usually due, in my opinion, to the pH or an actual compound sensitivity."

Larger molecular structures can heighten the possibility of allergies, whereas a smaller molecular compound, like a tiny peptide, would not likely set off such a reaction.

Instability of an ingredient is another cause leading to an allergic reaction or irritation. When unstable forms of vitamin C oxidize, the topical can change from an antioxidant to a pro-oxidant.

Rather than seeking chirally correct ingredients to avoid an allergic reaction, a better focus may be to opt for stable forms of ingredients. For example, BV-OSC is a stable, oil-soluble vitamin C derivative that has been shown to maintain a higher penetration rate and significantly higher collagen synthesis capacity without the stability or reactive issues of L-ascorbic acid.

This highly stable vitamin C derivative does not break down or oxidize until it penetrates the skin. Furthermore, BV-OSC protects against UVB and UVA cell damage; demonstrates a superior ability to synthesize collagen over L-ascorbic acid; and in vitro tests show that BV-OSC reduces melanogenesis by more than 80 percent.

Here again, a good delivery system can help offset potential reactions. PP-2, for example, is often used to deliver the active tretinoin (vitamin A) while minimizing irritation.

Unstable in its Foundation

The same science that is applied to pharmaceutical preparations cannot be applied explicitly to cosmetic formulations, and chirality is no exception. The very nature of the cosmetic formulation may change chiral isomers' rotation, thus changing the final results. According to Potini, most chirally correct ingredients degrade rather easily and change their chiral activity, which can then affect their penetration ability.

"Even if you put a chirally active in a cosmetic preparation, you cannot be sure that it will stay that way," Potini says. "These are very mobile materials. They are not inert and can change their rotations."

Whereas, pharmaceutical companies have the resources to ensure a high level of stability within their chirally correct formulations, many cosmetic manufacturers do not have the same level of research or resources to ensure that standard of stability. In fact, a chirally correct ingredient can change its rotation after a mere six months or a year, according to Potini. Cosmetic preparations have liquids, fats, esters, carriers, and alcohols that often degrade these chiral formulations, whereas drugs are mostly solids and are not as prone to the same degrading factors, he notes.

Lastly, it is important to keep in mind that no government regulations exist with respect to chiral compounds in cosmetics. "It is well-known that certain enzymes can process specific isomers and, in the case of a drug, that specific enantiomer would have to be specified for the dosage to be determined. In cosmetics, no such rule exists," says Pugliese. "The concept of chirality, as I see it, has no real future in skin care unless a great deal more research is done," says Pugliese.

Sam Dhatt is a world-renowned, award-winning cosmeceutical chemist who serves as the CEO and President of the product line DermaQuest Skin Therapy and of Allure Labs, a product formulation company, both of Hayward, CA. During his 20-plus year career as a sought-after formulator, Mr. Dhatt has developed and manufactured skincare products for over 700 companies, including many of the best-known brands in the industry. Mr. Dhatt is a frequent expert-author of articles featured in many trade journals and skincare publications and speaks often on ingredients and formulation with the goal of increasing the knowledge and success of estheticians.