The Research and Patent Wire

Recent advances in flavor and fragrance technology and investigation

A closer look at cocoa: Ducki et al. used headspace SPME and GC/MS to examine the aroma profile of cocoa products.[1] The authors employed a number of temperature conditions and extraction times for maximum recovery. The effect of distilled water or brine sample suspensions was examined to measure the effect on headspace composition. According to the report, "The SPME fiber coated with 50/30 µm DVB/CAR-PDMS afforded the highest extraction efficiency, particularly when the samples were extracted at 60°C for 15 min under dry conditions with toluene as an internal standard." The authors extracted and identified 45 compounds, dominated by previously known odor-active components. The authors reported that their cocoa product analysis was remarkably reproducible and sensitive, and that more research of the chocolate making process is underway to further analyze flavor/odor volatile compounds.

The mechanisms of perceived pleasantness: Small et al. set out to better understand the complex neuro-biological mechanics of how food smells perceived prior to tasting affect final flavor perception.[2] The authors focused specifically on the question of "whether the same neural circuits code for anticipatory and consummatory phases." The study findings conclude that anticipatory and consummatory chemosensation share some, but not all, mechanisms. The authors further noted that "perceived pleasantness" responses in the amygdala and thalamus likely reflect biology rather than learned preference.

Flavor preference learning: Capaldi and Privitera examined the mechanics of flavor preference using banana and almond extracts.[3] These extracts were combined with both liked (salt and saccharin) and disliked (quinine and citric acid) tastes and then mixed with polycrose before being subjected to two experimental flavor preference procedures. According to the authors, "The results showed that liked tastes potentiated preference conditioning to extracts … whereas extracts potentiated preference conditioning to disliked tastes. In both experiments, the presumably less liked stimulus (i.e., the extract in [the first experiment] and the disliked taste in [the second]) was the potentiated cue."

Color-flavor relationship in flavor perception: Levitan et al. examined color-flavor associations and how these associations affect human subjects' ability to distinguish the flavor of Smarties (Ce De Candy Inc.).[4] Participants were asked to judge whether pairs of the sugar candies had the same flavor or not. The results showed that color-flavor expectations affect flavor discrimination. The authors described their experiments as follows:

> We used pairs of Smarties that either did or did not differ in flavor. In making a sighted comparison between red and green Smarties, the participants were more likely to judge them as tasting the same if they believed all non-orange Smarties to be identical in flavor and as different in flavor if they did not hold such a belief. The ability of our participants to discriminate orange Smarties from the red and green Smarties was unaffected by their prior belief that orange Smarties taste different. In a second experiment, participants' ratings of their certainty of there being a difference in flavor between a red and an orange Smartie that either tasted the same or different were affected by their prior beliefs—those participants who expected a difference were more likely to report a difference than those without any such prior expectation.

Study claims to elucidate fragrance-allergic contact dermatitis link: According to Nardelli et al., "widespread use of fragrance-containing products is probably the most important reason for its high impact in allergic contact dermatitis."[5] The authors conducted a study tracking thousands of subjects over the course of 15 years in order to determine the frequency of fragrance allergen contact allergies. The results showed a variance in cases over time, with the face and hands as the most widely affected body sites. The authors concluded that contact dermatitis incidents can commonly be traced back to exposure to fragrance allergens.*

The authors outlined their study as follows:

> Patients/Methods: 10,128 patients underwent patch testing between January 1990 and December 2005 at the Dermatology department in Leuven. Results: 1,463 (14.5%)—380

*More resources on fragrance allergens: *ifraorg.org*; *rifm.org*.

(26%) males and 1,083 (74%) females—reacted positively to at least one fragrance-allergy marker in the standard series: 9% to fragrance mix I, 6% to *Myroxylon pereirae*, and 4.8% to colophonium (often in association), 2.1% to hydroxyisohexyl 3-cyclohexene carboxaldehyde and 2.1% to fragrance mix II, the latter 2 allergens having been introduced more recently.

Special Report: Triggering Controlled Release of Fragrance or Flavor**

This report examines some of the recent patent literature on triggers for controlled release of fragrance and is, itself, triggered by a reading of Andreas Herrmann's recent review of pro-fragrances in *Angewandte Chemie*.[6] Herrmann has worked for the past decade at Firmenich SA in Geneva, Switzerland, on the development of new fragrance delivery systems. He writes that current research interest in the flavor and fragrance industry is focused on the design of selective and efficient delivery systems with two goals: to control the slow release of highly volatile odorants in functional perfumery products; and to increase the stability of fragrance raw materials with unstable chemical functional groups such as aldehydes.[7]

Although some of the chemical triggers reviewed by Herrmann have already been commercialized (e.g., in the home care sector), many of them are still discussed mainly in the patent literature. Traditional triggers using an encapsulation approach have been commercialized by companies such as Salvona Technologies and Procter & Gamble and are more broadly discussed in the scientific literature.

This article will consider first some recent developments in fragrance release in encapsulated systems. Then, the controlled release of fragrances through the use of mild chemical reactions will be examined.

Encapsulated Systems

Encapsulation of active compounds into matrices or specifically designed capsules is the most widely used technique to prolong the longevity of the fragrance and, as an additional benefit, to increase the stability of unstable compounds in aggressive media, Herrmann notes.[7] Typically, the fragrance (or other functional ingredient) is protected inside the capsule until it is released by a trigger. Some triggers mentioned in recent patents include moisture, pH and temperature.

As an example of the variety of commercialized encapsulation possibilities, consider these platforms of controlled-release delivery systems developed by Salvona that can be used in a wide range of applications including pharmaceuticals, personal care and cosmeceuticals, food and nutraceuticals:[8]

- Hydrophobic submicron spheres, typically 100–400 nm in diameter, are used for long-lasting release of functional ingredients in aqueous systems, such as suspensions, creams and gels.[a] This product can be offered as a natural, synthetic, or blend of materials and has the ability to adhere to surfaces such as skin, hair and mucosa in rinse-off applications. In a dispersion, the system can be used in water-based products with and without surfactants. The release is controlled by the diffusion of the encapsulated active to the surrounding environment and by the partition of functional ingredients onto a targeted surface by solubility. This technology allows for targeted release due to hydrophobic forces and molecular recognition.

- Another submicron sphere system provides a large free volume core structure coated with synthetic polymers.[b] The spheres can be suspended in water or hydro-alcoholic environments that are ideal for spray-on or clear gel products to form a thin, invisible film containing the encapsulated actives. This product provides a long-lasting effect and, in some cases, moisture- and friction-triggered release. The release rate is modulated by moisture and governed by diffusion.

- Microspheres containing hydrophobic submicron-particles are designed for stability and to provide targeted, water-triggered or pH-triggered release.[c] The product can be made from natural, synthetic or blended synthetic polymers. The microspheres may also contain one or more functional ingredients that are encapsulated in different compartments and that can be adjusted to release the ingredients consecutively.

Moisture as a Trigger in Encapsulated Systems

A 2006 patent issued to Salvona discloses cosmetic products that impart a long-lasting cooling sensation and/or provide high impact fragrance or flavor burst in response to body moisture.[9] These performance features are achieved through the use of a multi-component, moisture-triggered, controlled-release system composed of solid hydrophobic nanospheres comprising cooling agents, fragrances, flavors and other active ingredients.

The nanospheres are encapsulated in a moisture-sensitive microsphere. The microsphere can comprise cooling agents, fragrances, flavors and other active ingredients. The fragrance, flavor, or active ingredients encapsulated in the moisture-sensitive microsphere are released upon exposure of the system to moisture occurring, for example, when the lips are wet or the body perspires. The cooling agents, fragrance, flavor or active ingredients encapsulated in the solid hydrophobic nanospheres are released over an extended period of time to impart a long-lasting cooling sensation, or long-lasting fragrance or flavor perception.

Suitable fragrances that can be used in this invention comprise, for example, the high-boiling components of woody/earthy bases containing sandalwood oil, civet,

**Reporting by Bud Brewster, Technical Editor,* Cosmetics & Toiletries *magazine*

[a]Commercialized by Salvona as NanoSal

[b]Commercialized by Salvona as HydroSal

[c]Commercialized by Salvona as MultiSal

Herrmann's Triggers

From his review article, these are Herrmann's classes and subclasses of triggers for the chemical release of pro-fragrances:[1]

Temperature

Oxidation

Light
- Photofragmentation
- Photoisomerization

Enzymes and microorganisms
- Glycosidases
- β-Lyases and amino acylaces
- Hydrolases

Hydrolysis and change of pH value
- Carboxylates
- Inorganic esters
- Silanes and siloxanes
- Acetals, ketals, and related structures
- Imines
- 1,4-Addition products

patchouli oil and other exotic materials. The perfumes can be of a light, floral fragrance, such as high-boiling components of rose extract or violet extract, or they can be formulated to provide a desirable fruity odor. An antiperspirant stick and a body spray are among the uses described for this system.

A more recent Salvona patent uses a similar carrier system—a free-flowing powder formed of solid hydrophobic nanospheres encapsulated in a moisture-sensitive microsphere—as disclosed in the previously cited patent, but the later patent addresses fragrance from an anhydrous cosmetic product.[10] It is intended to:

- protect the active ingredients, as well as the volatile constituents of the fragrances or flavors, during storage, until needed.
- provide moisture-triggered release, such as upon perspiration or wetting the lips, of the fragrances, flavors and other active ingredients that are encapsulated in the nanospheres or the microsphere's water-sensitive matrix.
- change the odor character or flavor character in response to moisture.
- provide prolonged release of fragrances, flavors and other active ingredients that are encapsulated in the solid hydrophobic nanospheres, over an extended period of time.

One example from this patent provides fragrance transition from floral to mint and delivers jojoba oil for an extended period of time. Menthol and jojoba oil are encapsulated in the hydrophobic nanospheres and a powder floral fragrance is encapsulated in the water-sensitive microsphere.

Another example describes a controlled-release system that encapsulates the same fragrance in both the solid hydrophobic nanospheres and the water-sensitive microsphere to provide both fragrance "burst" in response to moisture as well as to extend fragrance release over a prolonged period of time.

A 2007 patent issued to Haarmann & Reimer[°°°] (H&R) discloses a controlled-release encapsulated dry powder prepared from an emulsion by a simplified spray drying process.[11] The emulsion comprises a fully hydrolyzed polymer, a hydrophobic silica, a modified corn starch, at least one fragrance oil and water. The process begins by combining all the components in a single emulsion that can be spray dried, yielding an encapsulated dry powder that exhibits desirable solubility properties for use in deodorants or antiperspirants.

The preferred polymer is polyvinyl alcohol with a molecular weight from approximately 16,000 to 61,000. Spray drying removes the water and encapsulates microcapsules of the fragrance oil in the powder. For maximum effectiveness, the microcapsules should have dimensions of 10 to 250 microns, according to the patent.

The dry powder of this invention does not immediately dissolve upon contact with water and therefore is suitable in deodorant and antiperspirant compositions, preferably at levels between 0.5% and 5.0%. For example, deodorant sticks prepared according to **F-1** were compared to control sticks without the dry powder. The overall results showed that the fragrance encapsulated in the dry powder was reduced in its olfactive intensity when applied to the underarm, compared to the fragrance not encapsulated in the control sticks. The encapsulated fragrance also lasted longer than the fragrance in the control stick. In sticks aged at 45°C, the powder particles were found to be intact with undiminished effectiveness after one month.

Deodorant stick[11]	F-1
Dipropylene glycol	54.25% w/w
Propylene glycol	25.00
Water (*aqua*)	10.00
Triclosan	0.25
Sodium stearate	8.00
Encapsulated dry powder (PolyCap, H&R)	1.50
Fragrance (parfum) (H&R)	1.00
	100.00

Procedure: In a suitable vessel, combine A and heat to 75°C while mixing. Allow to cool during continued mixing. Add B to A while mixing. Pour AB into a suitable container and allow to cool.

In a 2006 patent application, Procter & Gamble describes its invention using encapsulation to deliver fragrance to skin and hair.[12] The idea is to generate

[°°°]This patent was applied for in 2002, previous to Haarmann & Reimer being folded into Symrise

so-called "fragrance-releasing complexes" of perfumes and other materials called "entrapment materials" that depress the volatility of the fragrances and allow a more controlled release over time. The production of such complexes allows the perfume to be retained on skin or hair until such times as its release is triggered. The "trigger" referred to may be a single factor such as externally applied moisture or pH change, or, in the case of skin, a combination of factors such as sweat and its components—urea, lactic acid and moisture—as well as sebum components such as cholesterol.

Entrapment materials according to this invention include polymers, capsules, microcapsules, nanocapsules, liposomes, film formers, cyclic oligosaccharides, materials capable of transforming the fragrances into pro-perfumes, and mixtures of these. Preferred are cyclic oligosaccharides, materials capable of transforming fragrances into pro-perfumes, and mixtures thereof. Highly preferred are cyclic oligosaccharides and mixtures thereof.

The concept of pro-fragrances in this invention is as follows. Pro-fragrances are fragrances that have been modified to suppress the volatility of that fragrance and delay its evaporation. Pro-fragrances may be synthesized from a given fragrance by conversion of that fragrance into a chemical species or reactive chemical form that releases the fragrance when the pro-fragrance is subjected to the proper conditions triggering breakdown, for example by hydrolysis. Synthesis may comprise reacting the fragrance with more than one type of entrapment material. These entrapment materials may comprise any one or more of a number of chemical groups such as acetal, ketal, orthoester or orthocarbonates. Depending on the pro-fragrance chosen, the trigger may range from contact with the acid mantle of, or enzymes in, the human skin to a shift in reaction equilibrium, a pH change or exposure to light. Once released, the fragrance has its original characteristics.

Theoretically, the use of fragrance-releasing complexes allows the possibility of selectively retaining perfumes of a given volatility, such as the elusive top-note fragrances. According to the inventors, this would open up a world of new possibilities: not only could fragrances be designed to have longer lasting top notes, but the evolution of a fragrance after application could be changed to give unique character combinations during the so-called "dry down" period.

Heat and Other Triggers

The inventions described so far give some suggestion about the variety of triggers for controlled release of fragrance from encapsulated systems. In addition to moisture, the following triggers have already been mentioned: friction, pH, temperature, sweat, sebum, light and enzymes.

An example of a heat-triggered fragrance delivery system is disclosed in a 2006 international patent application from National Starch and Chemical Company.[13] The invention delivers active ingredients and sensory markers out of nanospheres and onto hair, skin and fabric. The heat triggering in the hair care setting occurs during blow drying. The release rate of the active agents in the formulation is synchronized with that of the fragrance to convey to the consumer the product performance.

The controlled delivery system of this invention is a nanosphere, having an average sphere diameter of 0.01–10 microns. The nanosphere comprises hydrophobic materials, a cationic conditioning agent or a cationic conditioning agent in conjunction with a cationic charge booster to assist in adhering the spheres onto a surface.

Mild Chemical Reactions as Triggers

In encapsulated release, the encapsulation structure has to be breached somehow to release the fragrance volatiles. In chemical release, only a chemical bond in a fragrance precursor needs to be broken. That precursor, called a pro-fragrance or a pro-perfume, is a usually nonvolatile and odorless molecule suitably designed with a covalent bond that can be selectively cleaved in a chemical reaction releasing one or several volatile compounds. Herrmann calls this process controlled chemical release to distinguish it from the term controlled release, which he applies in the encapsulation setting.

In his *Angewandte Chemie* article, Herrmann gives this general description of those mild chemical reactions and the triggers that stimulate them:[7]

> To perform under everyday conditions, as for example during the application of a particular consumer product, the chemical reactions involved in these processes have to involve relatively mild reaction conditions that are defined by the environment. Typical triggers that may be used for mild chemicals are therefore quite limited. They mainly comprise variations of temperature, exposure to (day) light, easily accessible or ubiquitous reagents such as oxygen or water (including a change in the pH value), as well as different enzymes and microorganisms. Despite this limited number of "reagents," a broad variety of possible reactions has been used to generate a multitude of different volatile organic compounds.

Indeed, more than 120 pro-fragrance molecules are discussed in Herrmann's review, along with the volatile compounds they release. His classes and subclasses of triggers are listed in the sidebar (**see Herrmann's Triggers**).

Not all the precursors and triggers in Herrmann's review have stated applications in personal care, but here are several that do:

- Glycosidases from skin or skin bacteria can release a broad variety of fragrance alcohols from monosaccharides or disaccharides, and are therefore useful natural precursors for the enzymatic release of fragrances in cosmetic or body care applications.[14]
- Skin bacteria enzymes, in particular those of axilla bacteria, can transform odorless proteinaceous secretions into malodors. Up to now, several enzymes of

Corynebacteria or *Staphylococci*, namely pyrodoxal phosphate-dependent βlyases and Zn^{2+}-dependent aminoacylaces, have been identified that generate thiols or hexanoic acid derivatives, respectively. The knowledge of the enzymatic mechanisms in the formation of human body malodor helps in the development of new types of body care products and deodorants. Suitably designed fragrance precursors, which are cleaved by the malodor-creating enzyme to release neutral or pleasant odors, represent an interesting alternative to the use of antibacterial agents of enzyme inhibitors.[14]

- Water is the medium used for most perfumery applications. Hydrolysis, possibly induced by a change in the pH value, may thus be a suitable trigger to control the release of volatiles and to achieve an increased longevity of the fragrance perception. Typical examples are all kinds of washing processes where the product is stored under alkaline conditions such as soaps, or acidic conditions such as in body lotions and shampoos before being brought to a neutral pH value at the end of the washing cycle. In fact, most of the literature describing chemical delivery systems for volatiles is based on hydrolytic bond cleavage of a broad variety of different precursors.[15]

Herrmann concludes his review of more than 200 sources by noting that despite limiting the reaction conditions to small changes in the various triggers, a broad variety of different precursors have successfully been developed to control the release of volatile organic compounds by cleavage of a chemical bond. He writes, "Mild reaction conditions of our everyday environment are sufficient to trigger the cleavage of covalent bonds and thus allow organic chemistry—usually associated with flasks, solvents and special reagents—to be brought into common consumer products. The large number of patent applications published on this topic underlines the strong interest in pro-fragrance technologies."[16]

In an August 2007 patent, inventors at Procter & Gamble report their discovery that fragrance raw materials can be delivered by photo-labile pro-fragrance conjugates.[17] The photo-labile unit is a unit capable of releasing a pro-fragrance unit. The pro-fragrance unit, when released, is a fragrance raw material or it is a pro-fragrance compound capable of releasing a fragrance raw material. The conjugates are activated by exposing them to electromagnetic radiation, which is the initial step in a chemical cascade resulting in the ultimate release of a fragrance raw material. One of the steps in the cascade involves photochemically initiated fragmentation of a chemical bond between the photo-labile unit and a nitrogen atom contained within a pro-fragrance unit.

The inventors assert that this invention represents the first example of compounds that involve release of fragrances by way of a controlled chemical cascade initiated by exposure to electromagnetic radiation, especially UV light. The cascade, which begins the release of a fragrance raw material, may be controlled by requiring a certain wavelength of electromagnetic radiation to be present to initiate the release sequence. For example, "outside light," which typically comprises the full range of UV light, may be required to initiate the release of the fragrance precursor. In some cases, high temperatures may also initiate the chemical cascade.

The patent discloses methods of preparation of these four conjugates:

- Triplal oxazolidine conjugate
- Dihydro-β-ionone oxazine conjugate
- δ-Damascone Michael adduct conjugate
- bis-δ-Damascone Michael adduct conjugate

The patent also discusses methods of formulating these conjugates to deliver fragrances to laundry detergent compositions, fine fragrances, a personal cleanser, a deodorant gel stick and compositions for skin care and hair care. **F-2** is a shampoo and hair conditioning composition from the patent using βdamascone Michael adduct conjugate.

Shampoo and hair conditioner[17] **F-2**

Ammonium laureth-3 sulfate	14.00% w/w
Cocamidopropyl betaine	2.70
Polyquaternium-10	0.30
Paraffinum liquidum (mineral) oil	0.30
Cocamide MEA	0.80
Cetyl alcohol	0.42
Stearyl alcohol	0.18
Ethylene glycol distearate	1.50
Dimethicone	3.00
DMDM hydantoin	0.37
Additional free fragrances	1.00
δ-Damascone Michael adduct conjugate (see **Note**)	1.50
Water (*aqua*)	qs to 100.00

Note: *Prepared according to instructions in US patent No. 7,262,156 from Procter & Gamble*

Concluding Comments

At this stage, the appearance of the Herrmann pro-fragrance review article in a print journal is unusual because most of the discussion of controlled chemical release of fragrances is still in the patent literature. The same is largely true for the controlled release of fragrance from encapsulated systems, although this approach is older and more commercialized.

In this survey, Procter & Gamble was the only company with issued patents for both the encapsulated release and the chemical release systems. It has a ready outlet for fragrance in its vast array of products for personal care, household cleaning, laundry detergents, prescription drugs and disposable diapers.

Salvona Technologies has already commercialized many of its encapsulated systems for personal care, pharmaceutical, oral hygiene, nutraceutical and cosmetic products. The Alco Chemical Co. unit of National Starch

and Chemical Co. delivers fragrances in household product formulations using encapsulated systems.

This article could only touch on a few of the many companies and concepts involved in two aspects of the controlled release of fragrance.

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