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The Taste of Success

Choose your
drug flavor
carefully to
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THE TASTE OF SUCCESS

Choose your drug flavor carefully to improve patient compliance

COVER STORY BY
DAVID TISI

A well-constructed flavor system is crucial to oral drug formulations because it influences patient acceptability and compliance. Although sweeteners, flavor potentiators, and taste extenders are needed in a proper formulation, a flavored drug product typically requires an identifying flavor like orange, cherry, or mango. While only one piece of a flavoring system, the identifying flavor may be the one thing a patient most readily recognizes about a drug.

The flavor of a food or drug refers to the combination of the perception of taste, texture, and smell. Taste is more narrowly defined, referring only to those sensations perceived through the stimulation of receptor cells enclosed within the taste buds on the tongue, namely, sweet, sour, salty, bitter, and umami. Feeling factors, which include cooling, numbing, and burning sensations, occur when the free nerve endings in the mucous membrane are stimulated, in turn exciting the trigeminal nerve. In this way, feeling factors are more akin to a tactile response or chemical irritation. Other aspects of a flavor are perceived by the sense of smell.

The aroma of a product is caused by the perception of volatile chemicals that stimulate the olfactory region of the nose. The olfactory region is located at the top and back of the nasal passage and contains between 20 and 40 million odor receptors. Aroma chemicals can reach the olfactory region through multiple pathways. Orthonasal perception, commonly referred to as sniffing, involves volatile molecules traveling directly into the nose with inspired air. Alternatively, retronasal perception occurs when air is exhaled through the natural action of swallowing. In either case, the odors stimulate the olfactory receptor cells located in the epithelium of the nasal cavity. Electrical impulses then travel from the receptor cells along the nerve fibers to the brain, where they are interpreted.

Humans are thought to be capable of detecting more than 10,000 odor-bearing chemicals, though very rarely are these perceived individually. For example, there may be several hundred separate aroma chemicals that comprise the scent of a fresh piece of fruit. The aroma of a product is in fact the complex interaction of a multitude of individual aroma molecules.

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The difficulty involved in formulating a palatable pharmaceutical product typically stems from the taste of the active pharmaceutical ingredient (API), which can be bitter or excessively salty. Because the aroma of a product is perceived by a completely different mechanism than its taste, it is not physiologically possible for the aroma of a drug product to affect its bitterness in any meaningful way. The aroma is important in a palatable formulation, however, because it is the first attribute perceived and builds complexity by rounding out the flavor system.

THE FLAVOR BUSINESS

The flavor industry aims to reproduce natural aromas in a consistent fashion. A company that engages in the identification, isolation, concentration, and manufacture of these aroma chemicals is called a flavor house. As shown in Table 1 (right), the global flavor and fragrance industry adds up to about \$20 billion. A few large players dominate this highly fragmented industry, which is made up of hundreds of companies. The largest houses in the world generate about half of their revenue from flavors and half from fragrances, though smaller firms may specialize in one market or the other.

At the flavor house, persons responsible for the creation of these blends are known as flavorists. They are highly trained and skilled scientists who blend individual chemicals, reaction products, and natural extracts to create a desired aroma. There is limited academic education in flavor creation, so most flavorists are chemists, food scientists, or chemical engineers with further on-the-job specialized learning.

A flavor house creates and manufactures blends of aroma chemicals; each blend sells as an individual flavor. The intellectual property of a flavor house is the knowledge of the composition of these products. As such, flavors are sold as proprietary blends of aroma molecules, and the company purchasing the flavor doesn't know the actual composition of the flavor.

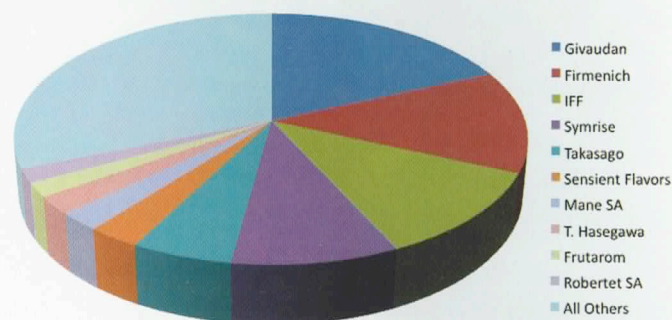
Just as a drug product is not only composed of the API, flavors are not only blends of aromatic molecules. Functional ingredients support the performance of the aromatic molecules. The comparison goes further. Because the API may only comprise a small percent of the weight of the final drug product, aroma molecules typically only make up 10% of the weight of a flavor.

The largest component of the remaining 90% is referred to as the "carrier." The choice of carrier determines the physical form of the flavor—dry or liquid. Typically, liquid flavors go into liquid

Table 1. 2007 World Flavor and Fragrance Market (Millions)

RANK	COMPANY	COUNTRY CURRENCY	= U.S.\$	MARKET SHARE
1	Givaudan	4,132 CHF	\$3,647.0	18.3%
2	Firmenich	~2,977 CHF	\$2,627.5	13.2%
3	IFF	2276.6	\$2,276.6	11.4%
4	Symrise	1274.5	\$1,860.8	9.3%
5	Takasago	¥124,231	\$1,112.0	5.6%
6	Sensient Flavors	~\$572**	\$572.0	2.9%
7	Mane SA	307.31	\$448.7	2.3%
8	T. Hasegawa	¥50,066	\$448.1	2.3%
9	Frutarom	368.3	\$368.3	1.8%
10	Robertet SA	241.14	\$352.1	1.8%
Top 10	—	—	\$13,700.0	68.9%
All Others	—	—	\$6,197.0	31.1%
Total Market	—	—	\$19,910	100.0%

Figure 1. Market Share of Major Flavor and Fragrance Companies

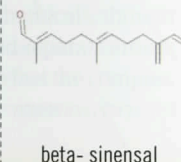
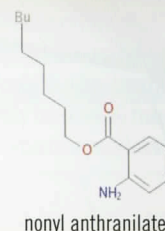
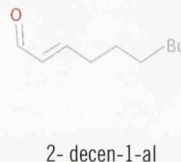
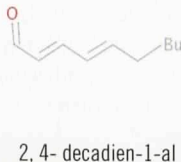


products; however, dry flavors may be used in either dry or liquid products. In a few cases, liquid flavors may be spray-coated onto a dry product, but these situations are the exception.

For liquid flavors, the carriers used are usually ethyl alcohol or propylene glycol. Ideally, these carriers serve as solvents that completely dissolve the aroma molecules into a stable solution. Less ideally, an emulsion may be required to deliver the aroma molecules. Emulsions or incompletely dissolved solutions may require that the bulk flavor be agitated before it is added to the final product; this requirement can be problematic from the standpoint of processing and product variability.

The manufacture of dry flavors begins with liquid flavors that are subsequently plated onto a dry carrier, generally maltodextrin, modified food starch, dextrose, or gum Arabic. Alternatively, these solids may be dissolved into the flavor solution and the mixture then spray dried. Due to the volatile nature of flavor molecules, these processes contribute to evaporation of the aroma

PRIMARY AROMA MOLECULES FOR ORANGE



chemicals, a process that changes the character of the flavor while adding complexity and cost to the process. Loss of volatiles is the primary reason liquid flavors are generally of higher flavor quality than dry flavors.

The carrier also serves to assure uniform dispersion of flavors throughout the product; regulate the strength of the flavor (the greater the carrier fraction, the weaker the flavor); fix the chemicals to assure aromas remain in the finished product after processing; and inhibit chemical reactions from occurring.

The remainder of the flavor formulation may contain additional functional ingredients. These include preservatives, which inhibit chemical reactions (typically antioxidants), microbial growth inhibitors, suspending agents, and emulsifiers.

FLAVOR SOURCES

Natural compounds are the first source for flavors. In a natural flavor, the flavorant must be extracted from the source substance (e.g., a natural strawberry must come from a strawberry plant). The methods of extraction can involve extrusion, solvent extraction, or distillation. To ameliorate the inherent variation of a natural product, extracts may be further purified and then fractionated to retain consistency.

Similar to natural flavors, natural with other natural flavors (WONFs) come from a natural source, but they may be blended with other natural flavors. A natural strawberry WONF may contain natural peach flavors, for example. WONFs tend to be less prone to variation in flavor characteristics, generally have more unique flavor profiles, and are usually cheaper to produce than their natural counterparts.

Artificial flavors are mixtures of individual synthesized aroma chemicals that may be identical to natural flavors. These flavors are combined together in ratios that successfully emulate a natural aroma. Because of increased purity and compositional uniformity, artificial flavors benefit from greater consistency (less batch to batch variation) and decreased impact from raw material changes. Additionally, artificial flavors allow more customization of the flavor profile.

Natural and artificial (N&A) flavors combine natural flavors with artificial flavors, without regard to the mass fraction of either constituent. It is commonly known in the industry that the composition of N&A flavors is mostly artificial.

Flavors are chemically labile compounds, degrading and changing in character over time. As a result, most flavor houses recommend that flavors be used within one year. Because artificial flavors are assembled from individual chemicals, more reactive species can be omitted from the blend. Thus, artificial flavors tend to withstand greater thermal stress during processing and have somewhat longer shelf lives than their natural counterparts. In all cases, prompt use and first-in, first-out logistics will assure the longest shelf life of the final product.

Table 2. Chemical Categorization of Flavor Molecules

CHEMICAL NAME	CLASS	ASSOCIATED AROMA
Allyl hexanoate	Ester	Pineapple
Benzyl acetate	Ester	Pear, strawberry, jasmine
Butyl butyrate	Ester	Pineapple
Ethyl butyrate	Ester	Banana, pineapple, strawberry
Ethyl hexanoate	Ester	Pineapple, waxy-green banana
Ethyl formate	Ester	Lemon, rum, strawberry
Ethyl heptanoate	Ester	Apricot, raspberry
Ethyl pentanoate	Ester	Apple
Geranyl butyrate	Ester	Cherry
Isobutyl acetate	Ester	Cherry, raspberry, strawberry
Isobutyl formate	Ester	Raspberry
Isoamyl acetate	Ester	Banana, pear
Isopropyl acetate	Ester	Fruity
Methyl anthranilate	Ester	Grape, jasmine
Methyl cinnamate	Ester	Strawberry
Amyl acetate	Ester	Apple, banana
Cinnamic aldehyde	Aldehyde	Cinnamon
Benzaldehyde	Aldehyde	Cherry
Geraniol	Alcohol	Rose oil
l-menthol	Alcohol	Peppermint
Terpinen-4-ol	Alcohol	Nutmeg

FLAVOR CREATION

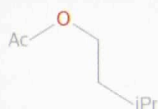
The number of known flavoring agents includes thousands of molecular compounds. There are three major classes of compounds in an individual flavor:

Impact compounds: These are individual compounds most representative of a flavor; that is, when smelled alone, these chemicals are reminiscent of the named flavor. These compounds represent most of the organoleptic potency of the flavor type. They are characteristic, essential, and necessary for the flavor. For example, methyl anthranilate is the impact compound of Concord grape; however, the flavor of methyl anthranilate by itself is not representative of a natural Concord grape.

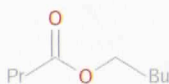
Contributory compounds: These compounds enhance the complexity and identity of the named flavor. They are not necessarily reminiscent of the named flavor; however, when used in conjunction with an impact compound, they bring the aroma closer to that of the named flavor. These may generate characteristics such as a “juicier” berry, or a “greener” apple.

Differential compounds: A flavor house may have tens of thousands of these aroma formulations to serve the food and fragrance market.

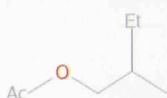
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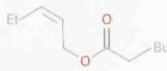
isoamyl acetate



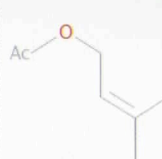
pentyl butanoate



2-methylbutyl acetate

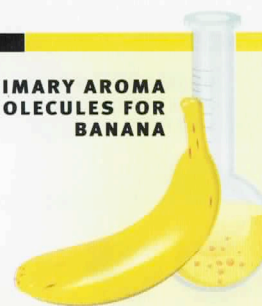


[(Z)-pent-2-enyl]
hexanoate



3-methylbut-2-enyl
acetate

PRIMARY AROMA MOLECULES FOR BANANA



(Continued from p. 17)

For each major flavor type (orange, strawberry, vanilla), the number of different flavor formulations at a single flavor house can be in the hundreds. The flavorist uses differential compounds to impart a distinctive characteristic to an individual flavor.

The number of individual aroma molecules that elicit an olfactory response may be in the thousands. These individual entities exist in a wide range of chemical structures, but some similarities can be found among them. Typically, aromatic molecules contain ester, ketone, and alcohol groups. For a lot of sweet and fruity flavors, many important aroma molecules have ester bonds in them. Meaty, earthy, and savory aromas more typically consist of sulfur-containing thiol groups.

FLAVOR REGULATION

The 1958 Food Additives Amendment to the Federal Food, Drug and Cosmetic Act delegated approval of safe compounds for use in flavors to an external body, the expert panel of the Flavor and Extract Manufacturers Association (FEMA), through its “generally recognized as safe” (GRAS) assessment program. The expert panel is made up of representatives from the fields of chemistry, toxicology, pharmacology, medicine, pathology, and statistics.

In a FEMA GRAS submission, the manufacturer submits a report to the expert panel. This report contains the flavor compound’s chemical, physical, and safety information, either from the scientific literature or from independent studies. Approval can take 12 to 18 months if the panel doesn’t request additional studies.

Additionally, a limited number of flavoring chemicals have monographs in the national formulary (NF) section of the USP-NF. These are commonly already used as components in the proprietary blends of chemicals sold by flavor houses and include vanillin, peppermint oil, and ethyl vanillin. While readily available and permissible in a drug product formulation, these individual compounds do not provide an acceptable flavor system when used alone. They may be used in combination with other flavors to create a palatable formulation, however.

Although not required by law, flavors may have a drug master file (DMF) on file with the Food and Drug Administration. As with all similar DMFs, these documents are not approved or rejected but “may be used to support an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), another DMF, an Export Application, or amendments and supplements to any of these.”

CREATE PALATABLE DRUGS

The key to formulating a palatable drug product is to build a complex flavor system that blends with and covers the negative sensory effects of the API as well as the excipients. Basic tastes

ameliorate other basic tastes, and beneficial aromatics are required to blend away negative ones. Proper masking of a drug product therefore requires an entire flavor system, one composed of sweeteners, taste modifiers, flavor extenders, and an identifying flavor.

The first step in formulating this flavor system is to develop a sweetener blend that has a sweetness time or intensity profile that matches the bitterness time or intensity profile of the API. Often, multiple sweeteners are selected from nutritive sugars, sugar alcohols, and artificial sweeteners. Descriptive sensory analysis panels are used throughout the process to evaluate the prototypes and provide guidance to the formulator, resulting in a formulation with balanced basic tastes.

The next step involves selecting acidulants, salts, and other taste modifiers and underlying aromatic supports that will carry the identifying flavor into the aftertaste. The goal is a base formulation in which all of the negative sensory attributes of the API and the functional excipients have been effectively blended away—a so-called “white” base, which is the underpinning of taste masking.

The final step is to formulate the identifying flavor. Because of inherent properties of the white base, some flavor types perform better than others, and this cannot always be predicted a priori. Hence, mandating a specific flavor type at the outset of formulation may lead to inferior flavor quality and is not recommended.

Each flavor house may offer tens or hundreds of flavors of each type, making selection a seemingly daunting—though not impossible—task. The first step is to evaluate the aroma of the candidate materials to eliminate those with inappropriate or undesirable characteristics (e.g., solventy, perfumey, or fermented). Then, evaluate the flavoring aromatics that pass the initial screen in the white base containing a GRAS mimetic or surrogate for the API. Next, eliminate flavor themes that are incompatible with the white base. For those that perform well, adjust usage levels to provide the appropriate flavor impact and duration.

The use of an API surrogate for flavor system development minimizes panelist exposure to drug product and rapid prototyping. Once final usage levels are determined, the mimetic should be replaced with the actual API for verification of the effectiveness of the flavoring system as a whole. Good clinical practices should be followed when evaluating API-containing prototypes to ensure the safety of the descriptive panelists.

Flavors are a crucial part of the flavor system of a drug product and, when used appropriately, lead to a balanced formulation. Most importantly, selection of an appropriate flavor requires knowledge of the physical and chemical properties of the product, input from marketing, and a system for appropriate evaluation. ■

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