Creating User-Friendly Oral Dosage Forms

The use of electronic tongue technology helps firms reduce development times and costs by overcoming challenges associated with traditional testing panels.

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Because of the inherently bitter taste of many active pharmaceutical ingredients (APIs), developers of oral dosage forms use taste-masking technologies and/or flavoring excipients to create products that are well received by patients and consumers. Human taste testing panels are commonly used to evaluate the success of new formulations, however, these suffer from a number of practical and ethical limitations. An alternative approach that can overcome these challenges and is gaining traction within the industry is the use of electronic tongues, which can detect and analyze the chemical components responsible for taste.

We talked to Detlev Haack, PhD, director of research and development, and Martin Koeberle, PhD, head of analytical development and stability testing, at Hermes Pharma to find out more about the importance of taste in the development of new pharmaceuticals and nutraceuticals, and how electronic tongue technology can reduce development times, lower costs and improve the reliability of results.

Contract Pharma: *Why is taste important to consider when developing new pharmaceutical or nutraceutical products?*

Detlev Haack (DH): It will probably not come as a surprise to hear that patients and consumers are more likely to take their medicines if they taste and smell good. Unfortunately, many APIs have an unpleasant taste; they can be very bitter, salty or sour, and even metallic or astringent.

Ensuring medicines taste pleasant, or at the very least acceptable, is extremely important in terms of improving patient compliance with treatment regimens. This is particularly true for user-friendly oral dosage forms, such as orally disintegrating granules (ODGs), chewable tablets and lozenges, which spend longer in the mouth and are tasted and smelled more intensely than conventional tablets and capsules. Take instant drinks and effervescent tablets, which are prepared as a drink; these must taste good in order to encourage complete consumption. And from a business perspective, developing an improved or unique tasting formulation can be a simple way of extending a product's lifecycle or differentiating a brand from the competition.

It is important to know how to use the latest technologies to mask the unpleasant taste and odor inherent with many active ingredients. For example, we use hot melt coating to create a physical barrier that prevents the poor taste of APIs coming through in the mouth. Combined with the addition of sugars, sweeteners and flavoring excipients if necessary, we can develop great tasting formulations that patients and consumers enjoy.

Contract Pharma: *What factors affect the taste of a formulation and how can they be utilized to develop great tasting products?*

Martin Koeberle (MK): First of all, it's important to say that developing the taste and aroma of a pharmaceutical product is not as straightforward as simply picking your favorite flavor at the ice cream parlor. The success of flavorings is dependent on factors such as the age of the target patient group and other consumer preferences that can vary substantially between coun-

tries. An often overlooked point is that the flavor of the medicine should support the therapeutic indication and work in harmony with the product itself. Some API and flavor excipient combinations work better together than others. Sour tasting APIs, for example, are best taste-masked with sour flavored excipients such as citrus or berry, rather than sweet flavorings such as banana or peach.

Having a firm understanding of the nuances of taste ensures the products developed meet the requirements of the target patients or consumers. Without this expertise and the scientific approach towards taste development, creating a pleasant or even neutral-tasting product would involve a lengthy trial and error process.

A key part of being able to develop good products efficiently is having a reliable way of assessing taste. The traditional approach for judging the success of taste-masking efforts is the use of human trials, where panels of individuals record their gustatory impressions in a questionnaire. While this approach is relatively straightforward for the development of foods and drinks, for medicines, this is significantly more challenging due to the ethical implications of giving healthy people substances that could potentially lead to undesirable side effects. Pharmaceutical taste testing is essentially a clinical trial—the process is often lengthy, tedious and costly, and only a few samples can be tested during each study. And, of course, if the taste of the test samples is not satisfactory, the whole process will need to be repeated.

Contract Pharma: *What solutions are there available for developers looking to more reliably evaluate taste?*

DH: Electronic tongue technology can be a very effective solution to the ethical and variability challenges associated with traditional taste testing panels. It supports developers in reaching a more definitive conclusion about the taste of their products much faster than would typically be achieved using traditional taste testing panels. Here, a significant amount of time and resources can be saved by eliminating the need for a lengthy human taste testing study, which must first be approved by an ethics committee, and is a very resource-intensive process.

Haack

Koeberle

Electronic tongues also enable developers to obtain a more reliable and comprehensive assessment of the complex mixture of organic and inorganic compounds that give substances their flavor. In addition to the five basic tastes of salty, sweet, sour, bitter and umami, electronic tongues can also detect metallic or astringent components. And unlike human testing panels, the data generated by the electronic tongue is not subjective, allowing a more reliable comparison of taste profiles to be made. This approach is particularly well suited for the pharmaceutical industry because electronic tongue instruments, methods and data can be qualified and validated.

Contract Pharma: *Could you describe the technology behind electronic tongues, including how they enable developers to better assess taste?*

MK: There are three essential parts to an electronic tongue: a potentiometric sensory array, signal receiving equipment, and a pattern recognition component. The electric signals produced by the potentiometric sensors are translated into taste patterns using statistical software. If this is done with a graphical assessment, the sensor data is presented in a radar plot, allowing the different taste profiles of products to be compared visually. Alternatively, the data can be processed using principle component analysis.

Electronic tongues require samples to be in liquid form for analysis, so you have to ensure that solid formulations are at least partially dissolved prior to analysis. Of course, it's important to replicate the physiological process as closely as possible. Dosage forms such as ODGs dissolve only partially in the mouth, so the analysis should only be performed on the fraction that dissolves before swallowing. In the lab, this can be recreated by adding 'artificial saliva' to the sample for a time similar to that which the ODGs would spend in the mouth prior to being swallowed. This partially dissolved mixture can then be filtered and analyzed using the electronic tongue. To assess a compound's aftertaste, the ODG can be dissolved completely and compared with the sample that was dissolved for the shorter amount of time.

Contract Pharma: *How are these taste profiles used to direct product development?*

DH: There are two options here, known as top-down and bottom-up approaches. In the top-down approach an existing product that has a desirable taste is identified, and then you would try to match the electronic tongue data for the product under development with the reference material as closely as possible. This approach is ideal when developing generic drugs where there is already a reference product to work with.

The bottom-up approach is used if there is no reference substance available. Here, a pleasant-tasting placebo is developed that can be tested by both the electronic tongue and a human tasting panel. Then, the formulation scientists attempt to recreate the same flavor in the drug product by adding flavorings and sweeteners to the API or by coating it. Success can be measured by comparing the electronic tongue data with that of the placebo. This way, the taste can be improved without the need for time-intensive taste studies.

Both of these routes can be very effective for the creation of products that are acceptable to patients and consumers. As electronic tongue technology continues to grow in use within the industry, I think we will see more companies adopting these kinds of approaches to formulation development. •

Detlev Haack, PhD, Director of Research & Development, Hermes Pharma, is responsible for the company's R&D projects, which include joint development of new pharmaceutical taste-masking formulations and related design manufacturing processes. Martin Koeberle, PhD, Head of Analytical Development & Stability Testing, Hermes Pharma, is responsible for the analytical aspects of development projects, including the evaluation and implementation of new analytical techniques and approaches.