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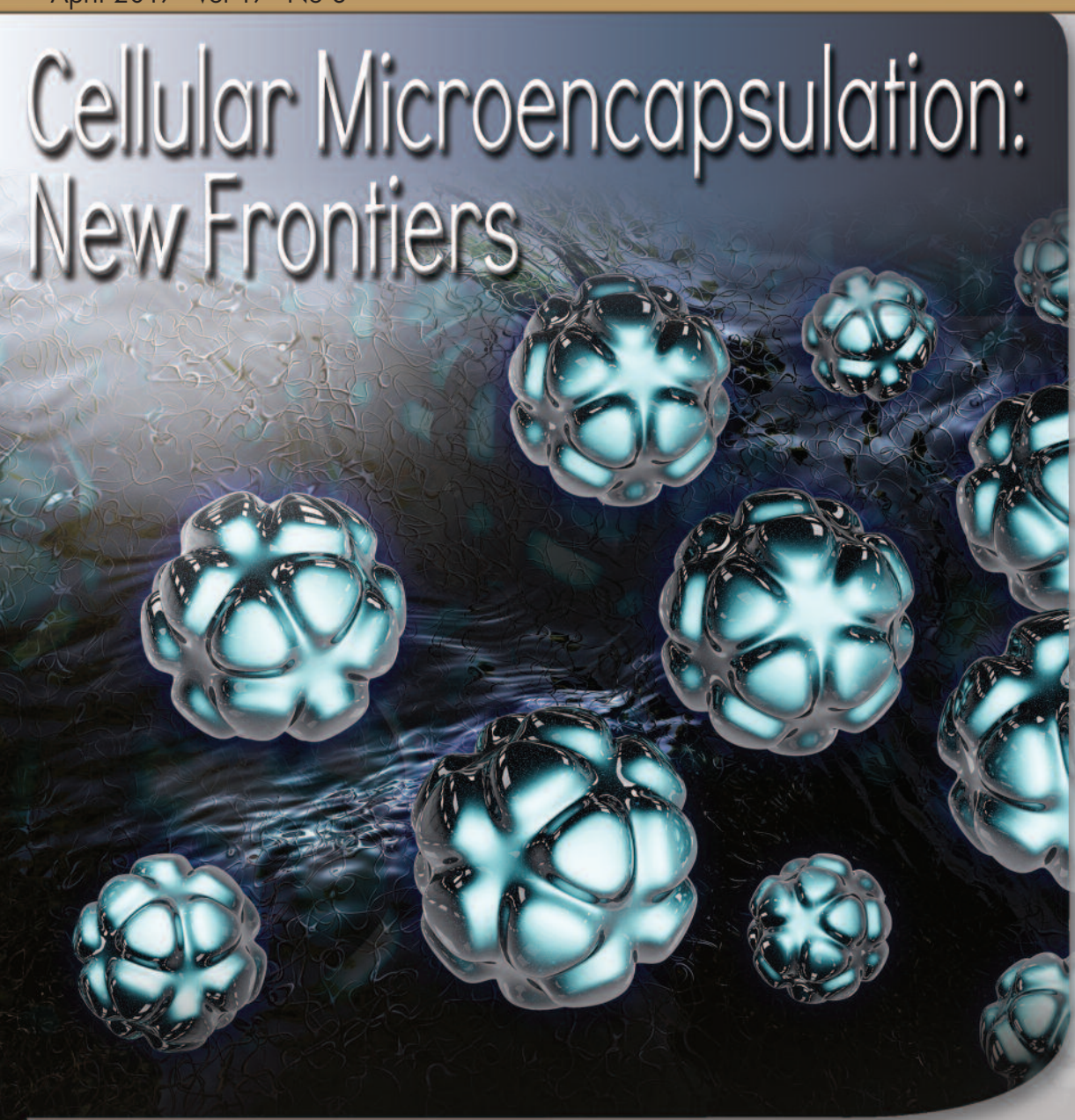

The science & business of drug development in specialty pharma, biotechnology, and drug delivery

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Improving the Palatability of User-Friendly Dosage Forms Using an Electronic Tongue

By: Detlev Haack, PhD

INTRODUCTION

User-friendly solid oral dosage forms are popular with patients and offer many benefits over conventional tablets. Rather than being swallowed whole, these dosage forms can be chewed, sucked, or dissolved in water and consumed as a drink. This makes them easy to swallow, even for children, elderly people, and those with dysphagia. As they tend to spend longer in the mouth and are tasted more thoroughly than traditional tablets and capsules, a pleasant taste is one of the key attributes that determines acceptability and patient compliance. However, even conventional tablets, which are normally considered by formulation scientists to taste neutral, are often perceived to taste unpleasant by patients and consumers, creating a potential barrier to uptake.

Given the inherently bitter taste of most active pharmaceutical ingredients (APIs), the challenge for the pharmaceutical industry is how best to use flavorings and taste-masking technologies to make oral dosage forms taste pleasant. Furthermore, the process of assessing taste raises both practical and ethical issues when relying on human tasting panels. One exciting alternative that is starting to gain traction in the industry is assessment via an electronic tongue to detect and analyze all the compounds responsible for taste within a sample. Electronic tongue instruments, methods, and data can be qualified and validated making this approach particularly suitable for pharmaceuticals. Electronic tongue analysis also means that taste evaluations can be incorporated into both stability studies and formulation development, potentially reducing drug development lead times and reducing costs accordingly.

THE CHALLENGE WITH CONVENTIONAL TABLETS & CAPSULES

While tablets and capsules remain a popular dosage form within the pharmaceutical industry, it is frequently underestimated how many people struggle to swallow them. In research recently conducted, it was discovered that more than half of the 2,000 people surveyed reported difficulty swallowing tablets and capsules, with around a third of these people describing the problem as serious.[1] There were a variety of reasons given for this with the most commonly cited being that tablets/capsules are too big,

FIGURE 1

User-friendly solid oral dosage forms offer an alternative to conventional tablets and capsules as they are easy to swallow – even for people with dysphagia and regardless of age. In addition, they are convenient and integrate well into daily routines.

TABLE 1

ADVANTAGES	DISADVANTAGES
Ethical & Safe No pharmaceuticals are consumed by humans until the clinical trial stage.	**Liquids Only** Solids must be dissolved prior to measurement.
Sensitive At least as sensitive as human taste.	**Sample Preparation** Samples (including reference and calibration samples) need preparation.
Scientific Approach Formulation scientists can replace a trial-and-error approach with a more efficient, effective scientific approach. Knowledge of complementary excipients and flavorings remains an important aspect though.	**Taste Only** The electric tongue makes no assessment of smell or texture, which humans often find difficult to distinguish from taste.
Consistent Data Electric tongue data is consistent and objective, unlike that generated from human tasting panels.	**Data Analysis** Expertise required.
Validated Approach The ability to qualify and validate the instrument, method, and data makes the electric tongue ideally suited to the highly regulated pharmaceutical industry.	**Maintenance** The electric tongue requires ongoing maintenance, including replacement and recalibration of taste sensors.
Rapid Data is available much quicker than via a human tasting panel, which must receive regulatory approval to proceed. A range of drug formulations can be screened in a short time.	**Upfront Cost** Requires an investment in instrumentation, plus training.
Access All Patients By removing the ethical challenges associated with human tasting panels, data can be provided for previously hard-to-reach patient groups, such as children and elderly people.	
High Throughput Analysis Could soon be possible.	

Advantages and disadvantages of using an electronic tongue for formulation development.

that they become stuck in the throat, or that they have an unpleasant taste or odor. Those surveyed did not experience similar difficulties swallowing foodstuffs or liquids.

When faced with tablets or capsules to swallow, people used various techniques to ease the process. 32% tried breaking them, 17% crushed them and dissolved them in water, and 9% chewed them. This is concerning as these approaches have the potential to negatively affect release profile, bioavailability, and medical efficacy of the API. Most worrying of all is that 8% simply resorted to not taking their medication at all.

Some people described other challenges with tablets and capsules. Older people often found it hard to press them out of the blister packaging, while younger people highlighted the inconvenience of taking them "on the go." User-friendly solid oral dosage forms offer a great alternative that overcome these issues (Figure 1).

Taste has been shown to be an important factor in how people perceive medications, and a negative experience can impact patient compliance. This is true for user-friendly dosage forms that spend longer in the mouth but also for conventional tablets and capsules. Thus, in order to develop a successful product, the pharmaceutical industry must ensure it tastes good.

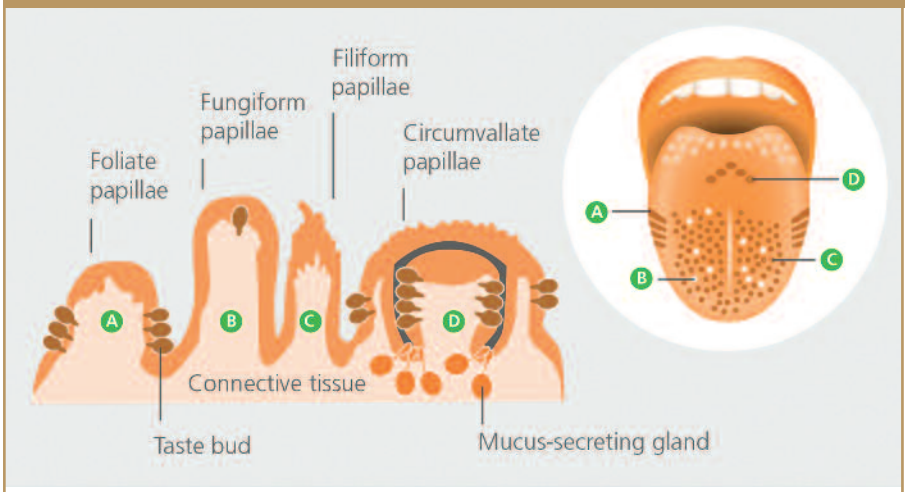
THE HUMAN SENSE OF TASTE

Humans rely on a combination of appearance, smell, taste, and texture to form a sensory impression for anything we consume. This is as true for pharmaceuticals as it is for foodstuffs. User-friendly dosage forms spend longer in the mouth than conventional tablets, making the sensory impression even more crucial.

For the pharmaceutical industry, appearance and texture are relatively easy to measure using various analytical instruments, as well as forming an assessment "by eye." All this can be achieved without unnecessary exposure to drug substances. Smell and taste, on the other hand, are harder to assess. A "sniff test" works well for some low-risk pharmaceuticals but would be unsafe for more toxic APIs. Likewise, it's possible, but far from ideal, to ask people to assess the taste of pharmaceuticals.

The human (or indeed mammalian) sense of taste is of evolutionary importance, and it's no exaggeration to say that it can be a life-saver. Toxic substances will often taste bitter while sweetness is usually associated with safe food and energy. Substances dissolved in the mouth stimulate taste receptors. These are located within taste buds, which are found around small structures called gustatory papillae on the tongue, soft palate, upper esophagus, and

FIGURE 2



The tongue comprises three types of papillae containing taste buds, plus the filiform papillae that only detects the texture of food.

epiglottis. We each have around 10,000 taste buds, although these are known to reduce in number as we age, particularly beyond the age of 50. As a result, we taste things differently later in life.

There are five basic tastes that are detected by taste receptors: saltiness, sweetness, bitterness, sourness, and umami (which corresponds to the flavor of glutamates and means "delicious" in Japanese and is often described as "savory" in English).

The complexity of how we taste creates an impression that lasts a long time (compared with smells, which are experienced for only a short time but are remembered well). This impression allows us to differentiate between initial taste and aftertaste – wine tasting notes provide a perfect example of this. Aftertastes may differ considerably from the flavor of what was consumed, and pose a particular problem for medicines.

We know that people taste differently and thus have different taste experiences of the same substance. This is not only caused by age but can also have genetic underpinnings. Based on an individual's taste bud profile, some tasters may be more sensitive to particular flavors than others. Likewise, some medicines and medical conditions themselves can alter people's perception of taste.

PALATABILITY OF PHARMACEUTICALS

To ensure both market success and patient adherence, it is important that all oral pharmaceuticals – but particularly user-friendly dosage forms – taste pleasant. When developing a new foodstuff, it's perfectly acceptable to ask a panel of people to assess the taste. For pharmaceuticals, however, this is more problematic. There are obvious ethical issues concerning giving a healthy person a medicine unnecessarily – particularly if it could have adverse pharmacological effects. Furthermore, molecules that are not FDA approved cannot be tested. A human tasting panel, therefore, can essentially be considered as a clinical trial and requires approval by an ethics committee. This makes it challenging and time-consuming to test even a few substances.

Most APIs have a particularly bitter taste, posing an additional obstacle for the pharmaceutical industry. Taste-masking must be employed – through addition of sugars, sweeteners, and flavorings, or use of coating technologies – to overcome this. At HERMES PHARMA, we know that formulation scientists experienced in taste-masking are able to make recommendations for which flavors to combine with which APIs and are also aware of which flavors are preferred in different geographies. For example, sour-tasting APIs are best taste-masked with flavors that include sour components. This means that citrus and berry flavors are suitable options but banana, caramel, and peach are not. Such expertise reduces the time spent in product development compared with a solely trial-and-error approach.

Today, the most common approach to assessing the relative success of taste-masking efforts, together with other organoleptic properties, is via a human tasting panel that records its immediate impressions on a questionnaire. However, due to inter-individual variability, sensory impressions are subjective – regardless of how well you train and calibrate your tasting panel. Most often, it is only possible to use healthy adults, which can also affect the results. Pediatric and geriatric patients are only permitted in exceptional circumstances.

ELECTRONIC TONGUE INSTRUMENTATION

A new instrument that is slowly starting to be adopted by formulation development scientists is the electronic tongue. This technology has been designed around how we know humans taste substances and can rapidly detect all the organic and inorganic compounds responsible for taste in a liquid sample. Sweet, salty, sour, bitter, and umami tastes are all tested for, together with metallic, pungent, or astringent components, and a taste profile is built accordingly.

Unlike human tasting panels, the data

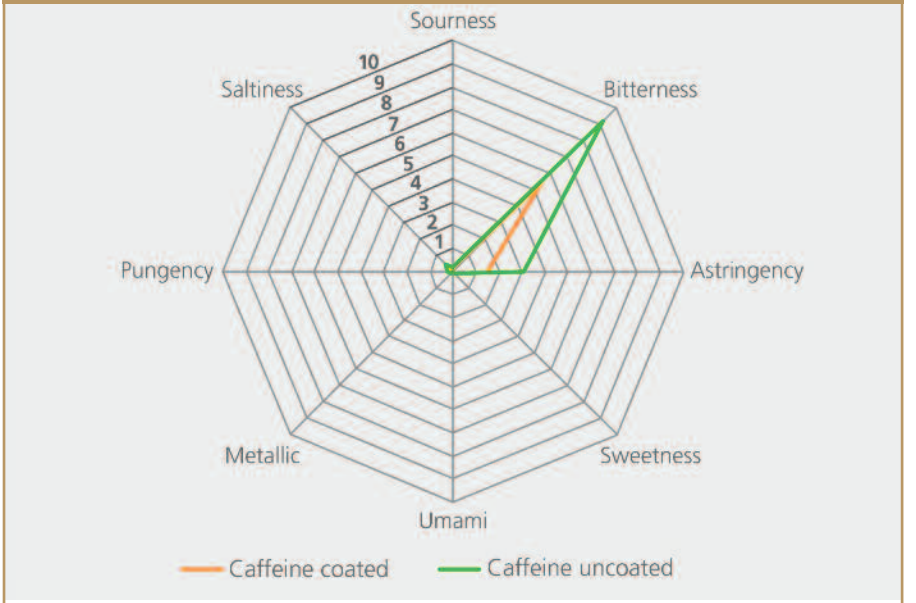
generated by the electronic tongue is not subjective, making it possible to reliably compare taste profiles between different substances. In fact, the instruments, methods, and data can all be qualified and validated, making this approach ideal for the pharmaceutical industry.

A significant advantage of the electronic tongue is that many more samples can be tested than via human tasting panels. This affords the opportunity to incorporate taste testing into stability studies and in formulation development – both of which can help reduce the time a product spends in development and minimize costs.

There are two electronic tongue instruments available on the market, although a number of academic institutions have developed their own versions for research purposes. Manufacturers are currently working on automating the electronic tongue and optimizing it for high throughput testing.[2]

Electronic tongues comprise three key components: sensory array, signal emitting/receiving equipment, and pattern recognition. The detection thresholds of the sensors are similar to, if not better than, those of human taste receptors. And the information provided by each sensor is complementary, with the combination of all the sensors providing a unique fingerprint for the substance being tested. Electronic signals, like those transmitted by nerves in humans, are generated as potentiometric variations. The electronic tongue uses statistical software as the "brain" to interpret and translate the sensor data into taste patterns. This can be done either graphically or mathematically. A graphical approach sees the signal from the various sensors added in a radar plot (Figure 3). Comparisons between different plots/substances are made visually. Alternatively, data from the different sensors can be processed mathematically via a multi-variate data analysis, such as principle component analysis (Figure 4). Either way, it is possible to compare the whole profile or just selected factors, such as sourness or bitterness, between different samples.

FIGURE 3



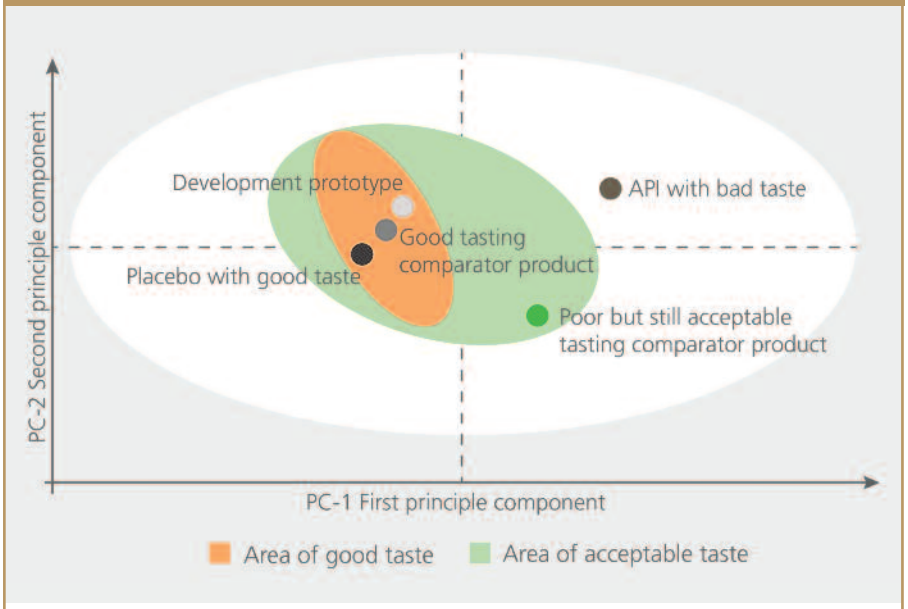
Comparison of caffeine before and after taste-masking. Taste characteristics were assessed on a scale from 0 to 10, where the stronger the characteristic, the higher the score. Hot-melt coating was used to significantly reduce the bitter and astringent taste of caffeine. While untreated caffeine cannot be formulated into an ODG, such taste-masked intermediates may easily be formulated into a pleasant tasting product.

It is important to note that only liquids can be analyzed using the electronic tongue. Solutions require no pre-treatment, except perhaps filtration. Solid formulations, however, must be at least partially dissolved before analysis. This dissolution step should replicate the physiological process as closely as possible. For example, as orally disintegrating granules (ODGs) will only partially dissolve in the mouth, analysis should be made on the fraction that dissolves before swallowing. This could be replicated in the laboratory by adding a known quantity of artificial saliva to the ODG for say 1 minute (the time needed to salivate and swallow the ODG in two to three gulps) and then filter to collect only the amount of the ODG that is dissolved in that time. Electronic tongue analysis can be performed on this sample. Aftertaste (to accommodate the few granules remaining between the teeth, for example) can be analyzed by dissolving the complete ODG and comparing it with the 1-minute sample. A similar approach can be used for tablets, which spend only seconds in the mouth before being swallowed with water. Only the film-coating is tasted with the tablet-core/API remaining undissolved.

GUIDING FORMULATION DEVELOPMENT

So, how can data generated through electronic tongue analysis be used to direct formulation development? One option is to identify a reference substance, one that is known to taste good, with the aim of re-creating the same taste (as closely as possible) with the product that is under development. When data is shown on a PCA plot, the final formulation should be

FIGURE 4



Principle component analysis (PCA) reduces large, multifactorial data sets so that differences between samples are highlighted and easier to compare. Using electronic tongue analysis, the flavor of a single product may comprise eight individual tastes. PCA is used to condense this data to just two principle components, which could be an individual taste (eg, sourness) or an abstract mathematical term (eg, bitterness² x astringency).

as close as possible to the reference product and/or placebo and distant from the original API. This top-down approach is ideally suited to the development of generic formulations in which there is an existing product that can be used as a reference substance. Ideally, there would also be supporting data available that demonstrates the market acceptance of the original product. Such data would be particularly advantageous if the product was targeted at a difficult to access market segment, such as pediatric medicines.

Alternatively, if there is no reference substance available, a pleasant-tasting placebo is created, which can be tested both by the electronic tongue and by a human tasting panel. Afterward, formulation scientists will attempt to re-create the same flavor in the drug product by adding flavorings and sweeteners to the API or coating it. Success is measured via comparing electronic tongue data with that of the placebo. This bottom-up approach carries the additional advantage that both the placebo and the drug product taste alike and so do not bias the results of later clinical trials.

SUMMARY

Regardless of whether a top-down or bottom-up approach is used, the goal is the same – to make the taste profile of a drug in development match that of a chosen, pleasant-tasting drug/placebo and to provide evidence of this via electronic tongue analysis. This analysis is more reliable and more consistent than the data generated using a human tasting panel. Human perception of taste varies considerably from person to person and often from day to day for an individual. It also allows pharmaceutical companies to employ a more ethical approach to assessing taste, by removing the need to administer medicines (that are still in development) to healthy volunteers. In addition, electronic tongue analysis helps to provide data for medicines targeted at hard-to-reach patient populations, such as infants and elderly people.[3] Having overcome the ethical problems of taste tests, the electronic tongue approach enables formulation scientists to perform more taste tests, and earlier in the formulation development process – with the dual benefits of shortening development times and reducing costs.[3] For these reasons, it is likely that we will see increased uptake of electronic tongue technology throughout the next few years. ◆

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BIOGRAPHY

Dr. Detlev Haack is the Director Research & Development at HERMES PHARMA. He earned his PhD at the University of Hamburg on the subject of Chemical and Physical Stability of Piroxicam in solid dispersion with PEG and PVP. In 1997, he received approbation as a pharmacist. From 2003-2007, Dr. Haack was Manager Sales & Business Development at Hermes Arzneimittel GmbH. He held the position of Associate Director R&D there from 2007-2012 before becoming Director R&D in 2013. His career includes a previous position as Head of Production at Altana Pharma Oranienburg GmbH.