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Removing the Bitter Taste from Drug Development

Integration of formulation development, real-time adaptive GMP manufacturing, and clinical testing using a consumer preference panel can save time and cost in performing taste-masking assessments.
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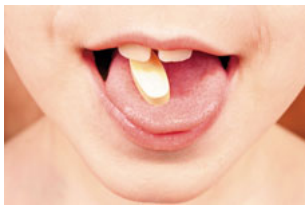

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The development of effectively formulated oral drug products is key to ensuring patient compliance and desired clinical outcomes. Given the increasing regulatory expectations for the development of bespoke age-appropriate products, critical performance features now include palatability and overall acceptability in addition to standard drug-delivery requirements for oral medications. Understanding and modifying the taste attributes of aversive drug substances is, therefore, important. There are several taste-masking techniques available, which involve either modification of the API itself or the formulation; however, there are as yet no standardized industry approaches for assessing whether the poor taste of a drug has been effectively masked.

Although *in-vitro* and preclinical methods can be applied, the resulting data are, at best, incomplete and, at worst, misleading. Approaches that have greater correlation with human response and, ideally, incorporate clinical assessment of the formulation are, therefore, required. This article reviews the breadth of taste-masking techniques available, the methods used to evaluate taste, and how an integrated approach to formulation development and clinical assessment can deliver significant benefits for product development and validation.

Compliance and the need for taste masking

The growing industry interest in palatability and acceptability of medicines is driven primarily by issues around patient adherence and compliance. Compliance is a particular issue with pediatric and geriatric patients (1), with certain medicines only achieving 11% compliance in children (2). These populations are not only the most sensitive to taste, but are also the patient groups who suffer most from dysphagia or have difficulty in coordinating swallowing, making the need to generate age-appropriate medicines imperative.

Regulators are now stipulating the requirement for pediatric investigation plans (PIPs) and pediatric study plans (PSPs) for all new registered products, making compliance essential to development. Demand is also growing at unprecedented rates amongst the ageing population. The World Health Organization estimates that the number of people aged 60 years or over is predicted to grow to 1.4 billion by 2030, and nearly 2.1 billion by 2050--more than double the number in 2015 (3). The so-called “silver tsunami” is poised to become one of the most meaningful social transformations of the 21st century.

Current approaches to masking taste

The palatability of a medicine is largely dictated by the taste of the API. A significant percentage of APIs on the market or in development are bitter tasting or unpalatable. In most cases, taste issues can be overcome by simply formulating the API into a tablet or capsule. This approach, however, cannot be used as standard in pediatric and geriatric populations because of swallowing difficulties associated with oral administration. Here, alternative formats such as liquids, suspensions, or dispersible or chewable products must be used.

A number of physiological and physicochemical approaches have been employed in an attempt to mask the taste of APIs and/or to prevent drugs from interacting with taste buds. These approaches fall into four main categories, outlined below and discussed in more detail in the paper published by J. Walsh *et al.* in 2014 (4).

API modification. API modification involves generating a new solid form or salt of the API, or administrating it as a prodrug. These approaches, however, are not always viable as the API may have just one stable form, or it may not be possible to form a salt with the neutral API.

Flavorings/excipients. Components such as sweeteners, flavorings, or solubility modifiers can be added to the formulation to overcome the taste of the API. This method is generally problematic for high dose APIs, where it may not be possible to mask the taste.

API complexation. The API can be complexed with a number of ligands to prevent the molecule interacting with taste receptors. These ligands include cyclodextrins, ion exchange resins, and polymers. This method is only possible with relatively low drug loading. The potential risk of altering the pharmacokinetic (PK) performance should also be considered.

Coatings on tablets/capsules. Coatings can be used to effectively cover the drug product and prevent the API from being released in the mouth. Coated formats, however, do not overcome issues with swallowing and lack of compliance. In addition, coatings add significant cost to the production process and may also affect the release and PK profile of the drug.

Beyond palatability and API properties, it is also necessary to consider broader drug-delivery needs when designing a taste-masked formulation. Factors such as requirement for solubilization enhancement; excipient stability limitations; patient age (and therefore the acceptable daily intake of excipients); whether the API must be taken with water or food; and impact on storage requirements (i.e., the need for refrigeration), all make the design of taste-masked formulations more complex, and the effective assessment of taste more important.

Methods used to assess taste

There is no standard industry approach defined for assessing and verifying whether a drug product's taste is acceptable. Although there is a range of commonly used techniques, outlined in **Table I**, the lack of standardization presents a significant issue in determining the taste of drug products.

Table I: Summary of methods used to assess taste.

Technique	Method(s)
Modeling/*in-silico* tools	*In-silico* bitterness databases (e.g., BitterDB) are used to predict the taste characteristics of drugs in development (5).
Animal models	Rodent brief-access taste aversion (BATA) model, where the rodents' lick patterns and frequencies are used to determine the palatability of a molecule. Frog taste-nerve response, where the nerve is connected to an AC amplifier and responses to a bitter drug, in varying formulations, are recorded. The peak height obtained is used to assess taste masking.
Analytical tools	*In-vitro* methods, such as ultraviolet (UV) spectrophotometry, involve suspending the taste-masked formulation in water and analyzing the API concentration. If the free API concentration is below a certain threshold, then the formulation is deemed to have sufficiently masked the taste of the API. Electronic or e-tongue sensors can be used to mimic human taste perception across the five major taste categories (bitter, salty, sour, sweet, and umami). During the assessment, the formulation or API is evaluated against a reference material (e.g., quinine hydrochloride as a bitter model compound). The taste patterns generated are then used to determine palatability.
Human taste panels	Groups of healthy volunteers are asked to taste a potentially aversive drug, and provide qualitative or quantitative information on several defined attributes to characterize taste and palatability parameters. Formulations are then developed with the aim of overcoming these challenges before a second assessment in human subjects to confirm acceptability. Selected formulation(s) can then progress (back) into clinical trials.

[2]

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All of the techniques, apart from human taste panels, are problematic in that they are surrogate methods, and, therefore, do not necessarily predict or match the human response. There is also additional time and cost associated with formulating and performing these surrogate analytical or preclinical tests. If the formulation is subsequently deemed unsuitable from a taste perspective in humans, further development cycles may be required, adding yet more cost and time to the process. It is, therefore, imperative that formulation selection is based on clinical taste assessments. Limitations can still be apparent if an acceptable formulation is not identified from the initial raft of prototypes prepared for human testing, highlighting a preferred need for a test model that allows flexibility to make compositional adjustments in real-time based on arising sensory data.

Rapid development and assessment of taste-masked products

The integration of formulation development, real-time adaptive GMP manufacturing, and clinical testing has been successfully used for both the assessment of taste and sensory attributes of drug substances, as well as the rapid screening of prototype taste-masked formulations. This model reduces development time and cost (given drug products are prepared within hours or days of dosing), and maximizes the potential for success, given adjustments to compositions are based on arising human clinical data (e.g., safety, tolerability, PK, pharmacodynamics [PD], or taste). As shown in **Figure 1**, flexibility can be enhanced by up-front definition of a formulation design space with bracketing ranges in the levels of critical-to-performance excipients.

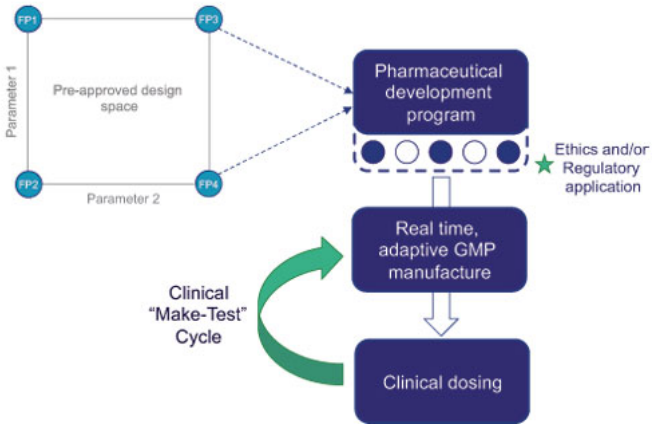

Figure 1: Quotient Sciences' integrated "make-test" cycle using a pre-approved, flexible formulation design space. [All figures are courtesy of the author.]

To perform the taste assessments, a consumer preference panel is established, typically of 12-18 subjects, using healthy adult volunteers trained in "sip and spit" tasting techniques. The emphasis of the panel is on "preference" rather than "measuring levels" of taste, providing representative data on acceptability of a formulation to a general population. Participants complete a bespoke questionnaire, consisting of visual analogue or hedonic scales to characterize a variety of API and formulation parameters, an example of which is shown in **Table II**. The scale will typically give seven ranking levels, ranging from "strongly like" to "strongly dislike." Several formulations can be assessed within a single day, with a one- to two-hour gap between tasting events.

Table II: Example consumer preference panel questionnaire.

Attribute	Strongly dislike	Dislike	Slightly dislike	Neither like nor dislike	Slightly like	Like	Strongly like
Smell							
Sweetness							
Bitterness							
Mouthfeel							
Texture							
Grittiness							
Difficulty to swallow							
Aftertaste							
Overall acceptability							

The program design and taste-assessment protocol are customized to the specific API and formulation in question. Design space variables can be established for API properties (e.g., particle size) or formulation attributes (e.g., levels of sweeteners, flavors, or viscosity modifiers). The protocol can also include assessments of API only (at single or multiple concentrations), positive controls (e.g., quinine for bitterness), the inclusion of replicate assessments to serve as further controls, and/or the use of multiple study periods to allow for interim analysis of data to guide decision making.

Performing these studies within the United Kingdom requires submission to and approval from an Independent Ethics Committee (IEC). Whether a regulatory review by the Medicines and Healthcare products Regulatory Agency (MHRA) is required will depend on study objectives, specifically if safety assessments are required.

Combining taste and pharmacokinetic evaluation

While taste assessments can be used as the sole clinical endpoint, they can also be combined with PK measurements as part of the same study. This approach can be particularly important if the taste-masking strategy has the potential to affect the PK performance of the existing (adult) formulation. The drug half-life requires a washout period, meaning that a taste evaluation can be incorporated into the study design without delaying the product assessment cycle (which is typically one to two weeks). The result is a powerful combination of clinical data confirming product palatability and acceptability, coupled with a full understanding of the PK performance in humans. In combination, this presents an ability to transition to efficacy studies in the target patient population with confidence, with an appropriate formulation, and with an informed dosage regimen.

The following case study demonstrates how the Quotient Sciences approach facilitated the rapid redevelopment of a taste-masked formulation for the long-term treatment of hyperkalemia (6).

Development and assessment of taste-masked formats for chronic disease

Background. Patients with heart failure or chronic kidney disease are at high risk of developing the potentially life-threatening condition hyperkalemia. The current approved treatment, sodium polystyrene sulfonate, has poor palatability and is unsuitable for long-term use. RDX7675 is a novel product being developed for the treatment of hyperkalemia. RDX7675 is a structural derivative of sodium polystyrene sulfonate and, therefore, shares some issues with taste and palatability. The goal was to expedite development of a clinically validated formulation for RDX7675, which suitably masked its taste, to enable its long-term use in the treatment of hyperkalemia (6).

Approach. Rapid screening of multiple formulation types and flavors was undertaken. All formats were manufactured within 24 hours of dosing requirements. A flexible clinical protocol ensured that any required changes to the formulation, flavor, or viscosity could be made within the study. A total of 18 subjects were included on the consumer preference panel in the two-period clinical study. Formulations were tasted every two hours, with doses expectorated, and palettes cleansed with water and unsalted crackers between tastings. Data were captured via questionnaires.

Output and impact. The flexible study design enabled real-time manufacturing and rapid taste assessments of multiple formulation options. Data from the consumer preference panel were available within nine weeks of program initiation. These data enabled the selection of a lead formulation to progress to the pivotal PK/PD clinical study (**Figure 2**).

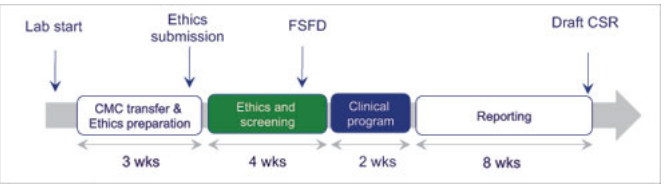

Figure 2: Summary of the development and clinical program for taste-masked formulations of RDX7675. CMC is chemistry, manufacturing and control. CSR is clinical study report. FSFD is first subject, first dose.

Conclusion

The need for taste-masked products continues to grow as a result of the significant number of unpalatable drugs in development and the requirement for age-appropriate delivery formats. The in-vitro and preclinical methods used to assess whether a formulation has effectively masked the taste of an API show poor correlation with human response, particularly where pediatric medicines are concerned (7). Where sensory human taste panels are used to quantify specific criteria with great precision, highly trained subjects are required, with the associated additional costs and timelines.

By integrating formulation development, real-time adaptive GMP manufacturing, and clinical assessments using consumer preference panels, formulations can be rapidly screened and their taste characteristics assessed. Acceptable taste-masked formats can be identified and optimized in real-time based upon arising sensory and/or PK data. Generated data can be used both to inform further development, as well as support compilation of PIPs and PSPs.

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