Quotient Sciences

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Information sheet

Developing a poorly tasting drug substance into a palatable dosage form

Introduction

Many drug substances are extremely bitter or have other aversive attributes, which can make developing palatable drug products extremely challenging. This is a common problem seen in medicines spanning all therapeutic areas, from antibiotics and painkillers to antihistamines and decongestants. The careful design and development of formulated oral drug products is key to ensuring patient acceptability and compliance for achieving the desired clinical outcomes.

Palatability can be influenced by several factors; the chemical structure of the drug substance, the finished medicinal product and by the excipients in the formulation. The European Medicines Agency (EMA) therefore advises that the taste attributes of the drug substance should be determined at an early stage in the development life cycle. This taste assessment can be made from dedicated adult testing panels or from literature, and regulators recommend that the palatability of a drug substance should contribute to the selection of the finished dosage form.

For oral pediatric medicinal products, palatability plays an even greater role in patient acceptability. Palatability is defined by the EMA as the "overall appreciation of a medicinal product in relation to its smell, taste, aftertaste and texture" (EMA CHMP 2014[1]). The Food and Drug Administration (FDA) define palatability in similar terms and state that "it is a critical factor in determining patient acceptance of oral dosage forms" (FDA CDER 2018[2]). Regulators worldwide are now stipulating the requirement for pediatric investigation plans (PIPs) and pediatric study plans (PSPs) for all new registered products, therefore taste assessment and taste optimization are of significant importance for the overall drug product development strategy.

Taste Assessment Techniques

Although there are no standardized industry approaches for assessing taste masking of a the poorly tasting drug substances, there are some techniques that can be utilized.

See Table 1 overleaf

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Table 1: Overview of taste assessment techniques used for drug product development.

Technique	Method
Modeling / in-silico tools	In-silico bitterness databases, for example BitterDB, are used to predict the taste characteristics of drugs in development
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 (active pharmaceutical ingredient) 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. 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.

In-silico, preclinical and analytical techniques present challenges as they are surrogate methods which may not predict or match the human response. Formulation prototypes derived from surrogate methods may subsequently be deemed unsuitable from a taste perspective in humans and further development cycles may be required, adding unforeseen cost and time to the process. It is, therefore, imperative that formulation selection is based on clinical taste assessments as early as possible in the development program. Limitations can still be apparent if an acceptable formulation is not identified from the initial raft of prototypes prepared for human testing, highlighting the benefits of a clinical test model that allows flexibility to make compositional adjustments in real-time based on arising sensory data.

Formulation Strategies for Taste Masking

The palatability of a medicine is largely dictated by the taste of the drug substance, or API. A significant number of APIs on the market or in development are bitter tasting or unpalatable and different physiological and physicochemical approaches have been used to mask the taste and/or to prevent drugs from interacting with taste buds. These approaches fall into four main categories (Walsh et al 2014[3]):

- **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.

A summary of formulation options is shown in Table 2.

Table 2: Summary of formulation options and taste masking strategies used at Quotient Sciences

Formulation	Taste-Masking Strategies
Solutions	Sweeteners Flavors Taste modifiers Complexation
Suspensions	
Powders and granules for reconstitution	
Orodispersible/chewable preparations	
Multiparticulates	Coatings
Minitablets	
Sprinkles	Food

Clinical Evaluation of Flavor

It is prudent to perform clinical taste assessments as early as possible in the drug development program. Translational Pharmaceutics® is an integrated GMP manufacturing and clinical testing platform used to perform rapid, adaptive trials in humans to assess and optimize taste attributes and/or PK performance. The design of taste assessment studies can include alternative flavors and sweeteners or different levels of a specific flavor and sweetener. Using Translational Pharmaceutics® it is possible to modify and optimize formulation compositions in real time in response to arising study data.

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 that formulation adjustments are based on arising human data such as safety, PK, and taste.

Volunteer Panels
Taste assessment methodologies for drugs and medicinal products in humans have been adopted from the food and drink industry. At Quotient Sciences, taste studies are conducted using healthy volunteers taken from the general population who are trained in tasting techniques. By using specially tailored questionnaires, and well-designed clinical protocols and the appropriate reference products, the aversive taste attributes of drug products can be assessed. By combining clinical expertise with drug formulation experience, our development teams will recommend the optimal formulation strategy for taste masking.

Sip and spit methodology
To avoid un-necessary exposure, standalone taste studies would usually be conducted as sip and spit studies with several taste assessments in any given day. Volunteers hold the formulation in their mouth for a given time period before the drug is expectorated, and a pre-defined taste questionnaire completed.

Data capture and analysis
Quotient make use of a customized 9-point Likert scale, assessing key taste attributes from dislike greatly to like greatly. This questionnaire has been customized in collaboration with our statistical group to ensure that the data analysis we perform on the results are robust in as small a population as possible, which helps minimize cost and time for these study types.

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.

Case study

Development and assessment of taste-masked formats for chronic disease

Background
The current approved treatment for hyperkalemia is sodium polystyrene sulfonate, which has poor palatability and is unsuitable for long-term use. RDX7675 is a new potential treatment and is a structural derivative of sodium polystyrene sulfonate, with the potential therefore to share similar issues with taste and palatability. The goal was to expedite development of a clinically validated formulation for RDX7675, which suitably masked its taste, for the long-term treatment of hyperkalemia[4].

Approach
Rapid screening of multiple formulation types and flavors was undertaken and real-time manufacturing was used with a flexible clinical protocol so that 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 and formulations were tasted every two hours. The clinical data were captured using volunteer questionnaires.

Output and impact
The flexible "make-test" program design enabled rapid taste assessments of multiple formulation options and data from the consumer preference panel selected a lead formulation to progress to the pivotal PK/PD (pharmacodynamic) clinical study. The overall program duration from laboratory formulation development to decision making clinical data was approximately 9 weeks.

Global Clinical Supply, Product Scale-up and Commercial Manufacture

Product scale-up and supply for patient trials
After the taste assessment is completed, Quotient can further optimize the formulation and efficiently scale-up manufacturing processes from pilot scale to larger scale to support late phase clinical trials and commercialization, with equipment trains from gram quantities to multi-kilogram batches for tablets and capsules.

From traditional large batch manufacturing, through bright stock distribution and personalized manufacturing, Quotient provides the full spectrum of clinical manufacturing and supply services. We have the expertise to support clinical packaging and labelling for worldwide clinical trials, with rapid turnaround so that studies can run smoothly and on-time. Our personalized manufacturing is highly bespoke and can be done on a per-patient basis, with customizable batch sizes which also conserves API and reduces waste in the manufacturing process.

Commercial manufacture
Quotient Sciences is a global player in commercial manufacturing of small molecule products including niche therapies such as oncology, orphan and pediatric indications. The experience we have from multiple successful launches allows us to accelerate development programs through registration and process validation. Our commercial production facility specializes in low-volume commercial products, support manufacturing batch sizes ranging from less than 1 kg to over 500 kg, with commercial batches up to 500 kg for solid oral dosage forms and up to 350 L for liquid formats. For customers preparing for ANDA, NDA, MAA or Japanese NDA, Quotient has the expertise and regulatory approval to manufacture registration and validation batches for the U.S., U.K., Europe and Japan. The Quotient team also has significant experience of supporting 505(b)(2) and all post-approval filings in a timely manner to supply the markets of intent.

References

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3. J. Walsh et al., Ad. Drug Deliv. Rev. 73 14–33 (2014)
4. V. Zann et al., Drug Des. Dev. Ther. 6 (11) 2663–2673 (2017)

Who is Quotient Sciences?

Quotient Sciences is a drug development and manufacturing accelerator providing integrated programs and tailored services across the entire development pathway. Cutting through silos across a range of drug development capabilities, we save precious time and money in getting drugs to patients. Everything we do for our customers is driven by an unswerving belief that ideas need to become solutions, molecules need to become cures, fast. Because humanity needs solutions, fast.

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