INDUSTRY INSIGHTS

Overcoming the challenges of taste masking

With many APIs exhibiting a strong, bitter taste, taste-masking is essential, particularly for pediatric patients. Dr Krizia M Karry, Head of Global Technical Marketing at BASF Pharma Solutions, discusses how taste-masking tactics have changed over the years and how to overcome some of the common challenges in the area.

Why is taste masking so important and how have approaches evolved over the years?

In a 2003 survey conducted by the American Association of Pediatrics, unpleasant taste was identified as the biggest barrier for completing treatment in pediatrics. Later in 2007, it was published that the average rate for compliance with treatment was only 58 percent in children, with major deterring factors attributed to formulation and palatability. These facts have helped to fuel advances in taste-masking technologies.

Initially, taste-masking relied mostly on the addition of sweeteners and flavors. The problem with this approach is that for very bitter compounds, such as ibuprofen, the bitterness will dominate because you can only include so much sweetener in a tablet without making it too large, or further masking the metallic taste of the sweetener. Another problem is in formulating APIs that are highly soluble and need to be administered in high doses (e.g., acetaminophen), because both the sweetener and drug will start to dissolve in the mouth, and the sweet and bitter taste receptors in the tongue will activate to trigger an unpleasant reaction in the patient.

Coating is an increasingly used technology that overcomes most of these challenges for aggressively bitter APIs, but coating does have its own caveats, such as ensuring minimal (or none) coating imperfections and adequate in-vivo drug release. Water soluble (e.g., polyvinylpyrrolidone and hydroxypropyl methylcellulose) and insoluble polymers (e.g., polyvinyl acetate and copolymers of methyl methacrylate) have been used in coating applications to achieve minimal drug release in the oral cavity and complete dissolution in the gastrointestinal tract.

Other taste-masking approaches have evolved over the years too, such as microencapsulation, the addition of pH-modifying agents and viscosity enhancers, suspensions, complex formations, solid dispersions, use of taste suppressants and potentiators, and dry coating bitter APIs. Although the use of these technologies has grown over the years, relative growth has been marginal compared to that of coating technologies.

What are the main challenges in using polymers to achieve effective taste masking?

The biggest challenge is identifying the right polymer – there is a lot to be considered! The formulator should take into account the API solubility, particle size, shape, dose and desired drug release pattern, as well as whether the polymer is water soluble/insoluble or if its solubility is pH-dependent. Formulators must also consider the polymer's hydration mechanism – is it swelling (delays diffusion of the bitter API) or gelling (increases viscosity to minimize contact between the active and the bitter tongue receptor), and other aspects such as coating film thickness.

The chemical and physical properties of the API play an important role when taste-masking. Its solubility, the dose at which it needs to be administered and the particle size and shape are very important considerations. A bitter API with a high solubility in saliva (pH 6.2 to 7.0) will be more difficult to taste-mask compared to an API with low solubility. Similarly, low particle size APIs in substrates with irregular shapes will be more difficult to coat than spherical ones. The dose is another important factor when utilizing sweeteners, microencapsulation or solid dispersion technologies for taste masking. High doses will limit the amount of sweetener that can be added to the formulation and polymer solid content when creating a solid dispersion.

What key innovations have helped alleviate taste-masking challenges?

There has been innovation in the polymers themselves and in materials combinations to achieve the desired taste masking performance. Also, patients will always prefer taking one dose instead of multiple doses to achieve the same outcome. In this regard, polymers that can mask bitter actives at high concentrations and/or be combined with pore formers for sustained-release applications (e.g., water insoluble polymers like polyvinyl acetate with gastrosoluble pore formers such as calcium carbonate) are gaining significant interest as a means to overcome taste-masking challenges.

At the same time, technologies have also evolved such that multilayer coating is now an alternative to formulate immediate and modified release drug products that contain bitter APIs.

BASF recently introduced a new copolymer that is suitable for taste-masking as well as moisture protection. Kollicoat® Smartseal (methyl methacrylate and diethylaminoethyl

methacrylate) is a film-forming polymer designed to be insoluble at typical saliva pH for efficient taste masking, but completely and immediately soluble in gastric (stomach) media at pH < 5.5. The polymer is available as an aqueous dispersion (Kollicoat® Smartseal 30 D) and as a powder (Kollicoat® Smartseal 100 P), which can either be redispersed in water or dissolved in organic solvents.

An additional consideration when selecting for the right polymer for taste-masking, is the material's cost-of-use. This includes taking into account any additional excipient that needs to be added to the formulation for the taste-masking to be effective, processing steps and times, current containment and safety measures, among others. In this case, Kollicoat® Smartseal outperforms all others because it was designed with the end-user in mind. The polymer is manufacturing site friendly because its processing is safe (does not require the addition of strong acids or harsh surfactants), it has a great smell, and it efficiently masks taste even at very low coating levels, which translates to material savings and process time reductions.

Are pharma manufacturers reluctant to use newer excipients?

Yes! Innovation in pharma excipients has been relatively slow. Some pharmaceutical companies see it as a gamble to utilize novel or innovative excipients in formulations because of the drug filing process. In the US, for example, excipients are regulated as part of the overall submission, rather than individually. Due to this, the natural tendency is to use novel excipients when all other options have failed or when its unique in its class. Nevertheless, innovation for excipients continues, with examples like Kollicoat® Smartseal for taste-masking and moisture protection and Soluplus® for the formulation of poorly water-soluble drugs via hot-melt extrusion technologies.

What can be done to make it easier for manufacturers to embrace innovation in ingredients?

Open dialogues between pharmaceutical manufacturers and excipient suppliers are very important, and the latter should work closely with regulators to push for faster updates to the FDA Inactive Ingredient Database (IID). The FDA defines a novel excipient as a material that has not been previously used in an approved drug product in the US (i.e., not listed in the IID) for the intended route and level of administration, or an excipient previously used in an approved drug product but now at a higher level of use than previously listed in the IID. Unfortunately, the IID database is only updated on a quarterly basis, and new registrations can be queued for months before they are visible to the public. This comes at an additional cost to innovators – an even longer return-on-investment. During this time, industry has no way to know if a novel excipient is acceptable for use early in development because no data is available prior to NDA approval.

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Where is there room for further improvement in taste-masking?

Forty percent of American adults have difficulty swallowing tablets, even though most have no problems with food or liquid. If you add to this a child's aversion to medications and note the increasing trend of companies to develop a drug product acceptable by all population segments (pediatrics, adults and geriatrics), then it's evident that effective taste-masking is crucial. Taste-masking approaches have advanced significantly but I'd like to see more innovation in taste-masking new technologies for dosage forms such as multi-unit pellet systems (MUPS), chewables, gummies, orally dissolving tablets and films, and sachets. Currently, there are few polymers that can efficiently accomplish this, but as expected, published applications are scarce to maintain a competitive advantage.

For more information or to connect with a BASF expert, visit our website at **pharma.basf.com.**