taste masking

Bitter to Better: Formulation strategies for effective taste masking

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The development and optimization of taste-masking formulations, especially for pediatric drug products, continues to be an important aspect of solid oral dosage formulation. This article examines several techniques to overcome the bitter or unpleasant taste of some active pharmaceutical ingredients.

Although many effective pharmaceutical treatments exist, a recent Institute of Medicine report identified a gap between actual treatment success rates and those believed to be achievable. This gap has been attributed partly to a lack of patient adherence to recommended medication regimens [1].

Multiple factors, including costs, medical condition, and complexity of regimen, play a role in adherence rates. Lack of patient adherence often leads to worsening health and poor outcomes and increases costs across the healthcare system. Taste masking can contribute to improved drug acceptability and medication adherence, particularly in pediatric, geriatric, and other special patient populations. This article describes current taste-masking methods and highlights areas where effective taste-masking formulation techniques can play a role.

Basic considerations for taste masking

When the taste and palatability of a drug product's active pharmaceutical ingredient (API) is likely to be

unpleasant to patients or when the dosage form has a high degree of interaction with patients' taste buds (such as with chewable and orally disintegrating tablets, gums, and gummies), taste masking is likely to be beneficial.

For the formulator, the key initial consideration is the level of masking required, which depends on the API and the dosage form design. In some cases, the API is only slightly bitter and can be masked easily with flavors and sweeteners; in other cases, the API has a very bitter taste requiring additional taste-masking techniques. For general use tablets, which the patient swallows whole, an immediate-release film coating is typically sufficient to mask an unpleasant API. With bitter APIs, however, even a small amount of exposure is sufficient to give the patient a perception of bad taste. In these cases, formulators should consider using a barrier membrane coating or other alternative technique to mask the taste of the drug particles or granules.

Dosage strength may dictate whether a specific taste-masking formulation strategy is suitable. Low-dose APIs are easiest to mask, while high-dose APIs pose a problem simply because more material (and a greater surface area) needs to be masked. This is especially true for formulations with fast-dissolving bases, which may leave patients with a mouthful of coated API particles that produce a gritty mouthfeel. These particles can also get stuck between the patients' teeth, producing a lingering grittiness and bitterness as further chewing breaks the coated particles. In pediatric formulations, the dose is generally small enough to allow flexibility with respect to the taste-masking approach.

The physicochemical properties of an API also play an important role when selecting a taste-masking technology. For example, certain APIs have lower solubility at different pH values. Adding an alkalizing agent (such as sodium bicarbonate) or an acidifying agent (such as citric acid) can reduce solubility in the mouth, minimizing taste perception. You can also use a lower-solubility form of an API to reduce or eliminate poor taste. With a lower-solubility form of ranitidine base, the bitter taste can be adequately masked by flavors and sweeteners, but for more soluble forms of ranitidine (such as ranitidine hydrochloride), flavors and sweeteners may not be sufficient, particularly if the dosage form is an orally disintegrating tablet (ODT).

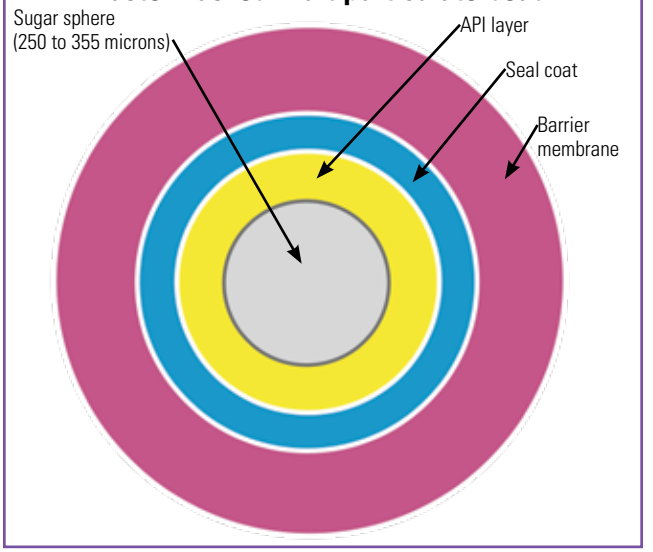
Impact of substrate properties

Processing and taste masking is more difficult for APIs with fine particles rather than coarse particles, and successful coating is easier when the particles have a narrow particle size distribution. The ideal particle shape for coating is a sphere; as sphericity increases, surface area decreases, producing more uniform coating.

For taste-masked particles, the ideal size range is 100 to 400 microns, with an average (d50) particle size of approximately 200 to 300 microns. Excessive fines are prone to agglomeration during coating operations, which poses processing challenges and reduces yields, while coarse particles are prone to leaving a gritty mouthfeel. Irregularly shaped or rod-like particles will result in areas of thicker and thinner coating along particle surfaces, requiring greater overall coating use and film thickness to ensure adequate coverage.

FIGURE 1

Taste-masked multiparticulate bead



Flavors and sweeteners

Flavors and sweeteners are adequate to mask the unpleasant taste of many drug products. Both natural and artificial flavors are available and are typically included at concentrations lower than 3 percent. Natural flavors tend to offer better taste, but artificial flavors are easier to characterize and are more chemically stable. In general, a combination of flavors may be used to complement an API's taste profile, and the flavor selection should be based on the taste characteristics of the API. Acidic APIs are more successfully masked using flavors such as citrus and berry, while alkaline APIs are better suited for flavors such as banana, caramel, cherry, and licorice.

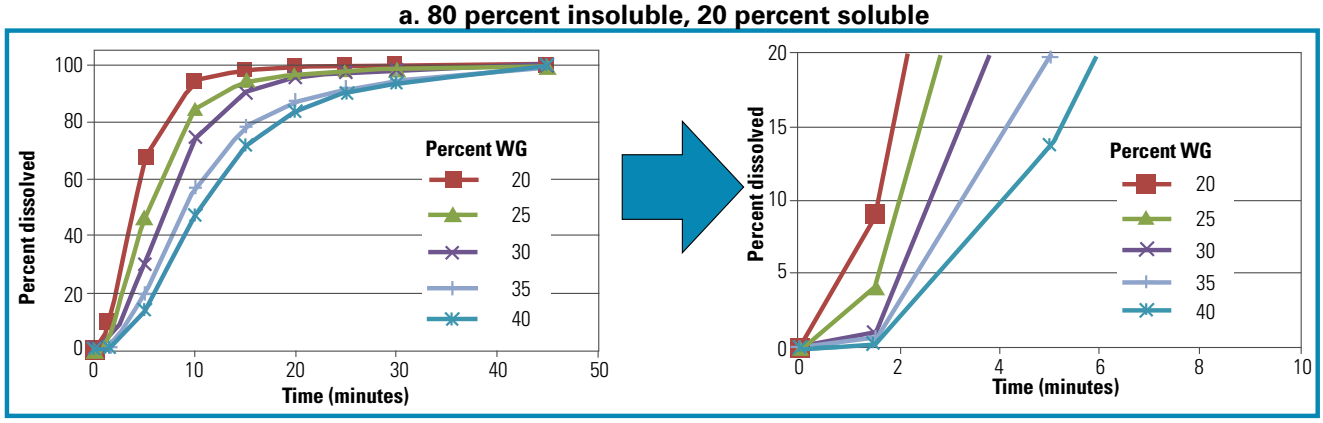
At levels of 40 to 70 percent, natural sweeteners such as mannitol, dextrose, and xylitol provide body and texture to the product, while artificial sweeteners such as sodium saccharin, acesulfame potassium, aspartame, and sucralose provide an intense sweet taste at lower concentrations (generally less than 1 percent). Each sweetener has advantages and disadvantages in terms of taste and texture, and formulators often combine sweeteners in a single dosage form to provide sufficient sweetness and intensity to mask an unpleasant-tasting API.

Another strategy to aid taste masking is to add bitter blockers, which are receptor antagonists that bind competitively to specific bitter receptor sites in the patient's mouth, blocking the release of proteins responsible for taste transduction. These antagonists are often tasteless compounds that are close structural analogues of the API.

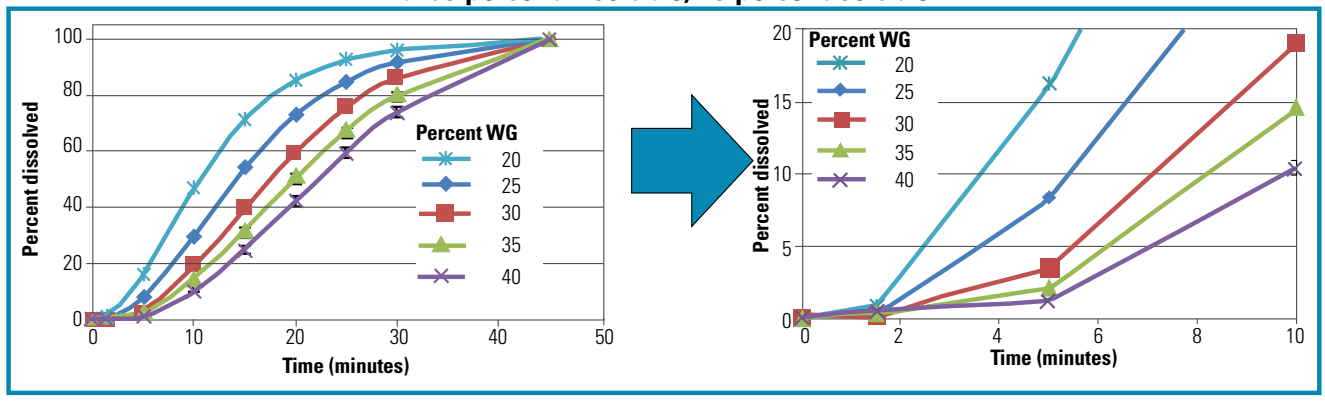
FIGURE 2

Release profiles for multiparticulates coated with combination water-insoluble and water-soluble polymer coatings

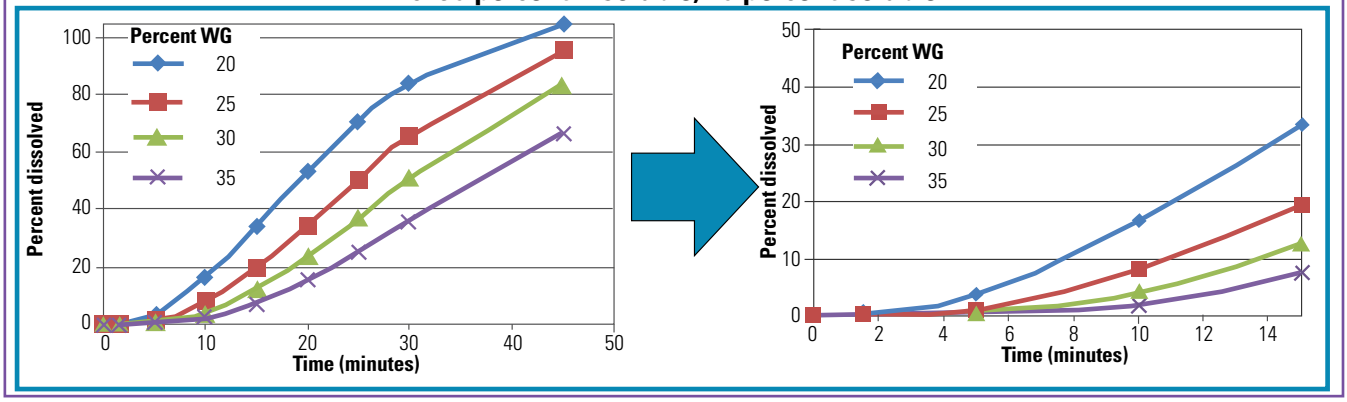
a. 80 percent insoluble, 20 percent soluble



b. 85 percent insoluble, 15 percent soluble



c. 90 percent insoluble, 10 percent soluble



Formulation strategies

Formulators generally consider well-known and widely accepted ingredients, polymers (or coatings), and manufacturing methods when determining the right taste-masking strategy. Taste-masking polymers can be broadly categorized into two categories, pH-independent and pH-dependent.

For pH-independent release coatings, both water-insoluble and water-soluble (hydrophilic) polymers are available, including ethylcellulose, cellulose acetate, hypromellose, and hydroxypropyl cellulose. For these systems, taste masking and API release is based on time-dependent diffusion, where polymer combinations are empirically determined to provide the desired degree of taste masking and release. These systems enjoy wide regulatory acceptance, ease of use, stability, and minimal risk of bio-performance issues.

pH-dependent systems include reverse enteric polymers. These polymer systems are soluble under acidic conditions, with ideally little or no release under neutral to alkaline conditions. This provides protection in the patient's mouth, where the pH is higher. pH-dependent taste-masking approaches require careful consideration to mitigate possible variation in release performance depending, for example, on food types used for delivering the product to pediatric patients. Another key consideration when using this approach is the potential impact on bio-performance.

FIGURE 3

Equilibrium reaction mechanism between ion exchange resin and API

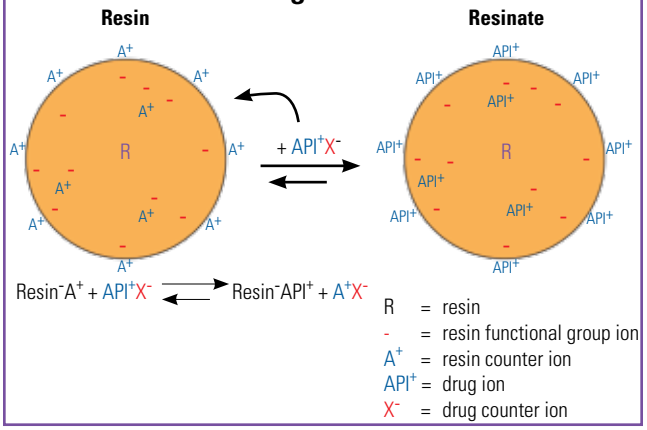
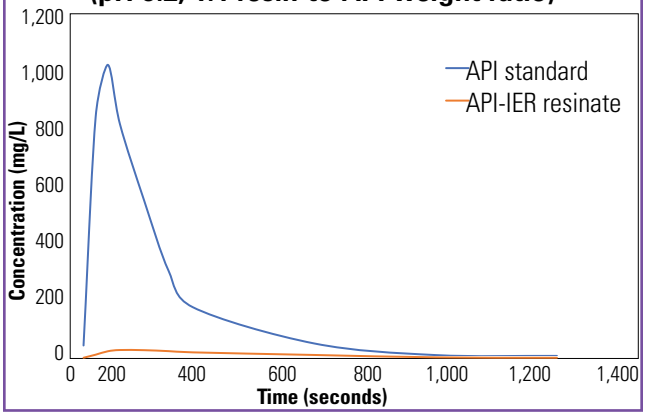


FIGURE 4

Dissolution of a BCS Class I sparingly soluble API using an ion exchange resin in simulated saliva (pH 6.2, 1:1 resin-to-API weight ratio)



Barrier membrane polymer coatings

A barrier membrane polymer coating can provide acceptable taste masking and palatability depending on the API's particle size, particle size distribution, and morphology as well as the coating composition and film thickness. Applying the polymer coating directly to API particles or API-layered substrates is the most common and well understood method for taste masking a bitter API [2]. The polymer is applied via spraying or powder layering to form a barrier membrane to the substrate, reducing or eliminating API release within the patient's mouth.

Fluid-bed coating is often the unit operation of choice for this type of application because it's efficient; applicable to particles, granules, and layered substrates; provides a uniform, continuous product coating; can be used in aqueous, organic coating, and powder layering applications; and is suitable for containment of potent compounds.

In a series of studies, Colorcon researchers combined a water-insoluble ethylcellulose dispersion type B NF coating (Surelease) and a water-soluble hypromellose-based coating (Opadry) at ratios of 80:20, 85:15, and 90:10 Surelease-to-Opadry (w/w) and applied the resulting combination coatings to a BCS Class I sparingly soluble API granule or layered substrate [3, 4]. In the case of the layered substrate, successive layers of API and coating were applied to a sugar sphere (Suglet) resulting in a taste-masked multiparticulate bead, as shown in Figure 1.

The researchers coated the API-layered multi-particulates to 4 or 5 different weight-gain (WG) levels between 20 and 40 percent, applying a seal-coat between the API layer and the functional layer to protect the API layer from erosion and moisture and provide a uniform application surface for the functional layer. (Depending on the extent of desired taste masking and the API release profile, a swellable component can be added to this seal-coating layer to aid in rupturing the barrier membrane coating.)

The dissolution profiles for the coated multi-particulates are shown in Figures 2a, b, and c. The results illustrate how, when either the coating thickness (percent WG) or the percentage of water insoluble polymer is increased, initial API release is slowed and terminal release is extended.

While taste-masking applications strive for minimal to no API release in the patient's mouth, they often also require immediate release functionality to achieve bioequivalence.

These study results demonstrate how formulators can achieve effective taste masking with an initial lag in API release yet still retain the desired immediate-release behavior.

Ion exchange resins

Ion exchange resins (IERs) are insoluble polymers with acidic or basic functional groups, capable of exchanging counter-ions with surrounding media, as shown in Figure 3. In industrial and domestic water treatment, this ion exchange involves low-molecular-weight minerals such as calcium and magnesium (demineralization). In the pharmaceutical industry, this exchange applies to larger organic ions with molecular weights up to several hundred daltons and occurs both *in vitro* and *in vivo*.

IERs are insoluble in all solvents and at all pH values, which, combined with their high molecular weight, prevents them from being absorbed by the body and makes them safe and nontoxic. Pharmaceutical developers have been using IERs for many years as both excipients and pharmacologically active ingredients. IERs can perform several functions, including modifying API release, taste masking, and improving API stability, and they are suitable for a variety of solid oral dosage forms, including ODTs, chewable tablets, fast-melt formulations, thin film strips, gums, gummies, and stick packs as well as liquid formulations.

IERs are effective for taste masking because the API-IER complex (called the resinate) is insoluble, which prevents the API from directly contacting the taste buds.

Additionally, the small particle size of IER polymers produces a less gritty mouthfeel, improving the palatability of taste-masked formulations. For these reasons, IERs can achieve an effectiveness and duration of taste masking that's not possible with other methods, as demonstrated by the example in Figure 4. In this example, a BCS Class I API was combined with an IER (AMBERLITE [5]) at a 1:1 API-to-resin ratio (w/w). The resulting resinate achieved a taste-masking duration of 20 minutes and a taste-masking efficiency of 94 percent, which was calculated as the C_{max} of the API-resin complex divided by the C_{max} of the API and expressed as a percentage.

IERs have a long history in pharmaceuticals dating back to the mid-1950s and their use enhancing the stability of vitamin B formulations [6]. One of the most well-known IER applications is for taste masking liquid antitussive and cough suppressant preparations, such as Tussionex [7] and Delsym [8]. IERs offer several advantages over other approaches to taste masking, including:

- High taste-masking efficiency for extended periods of time;
- Ease of scale-up from laboratory to production;
- Applicability for liquids and suspensions;
- Excellent palatability and less gritty mouthfeel;
- Elimination of breakthrough taste.

Summary

Taste-masked formulations can be challenging to develop, and the best method is often dictated by the API's physicochemical properties and taste profile. Fortunately, effective methods, such as flavors and sweeteners, barrier membrane coatings, and IERs, are available for use individually or in combination, depending on the application. While the methods and polymers may vary, coating remains the preferred method for masking bitter APIs and improving patient experience. *T&C*

References

1. A. M. Peterson, L. Takiya, and R. Finley, "Meta-analysis of trials of interventions to improve medication adherence," *American Journal of Health System Pharmacists*, Vol. 60, pages 657-665, (2003).

2. Zelalem Ayenew, Vibha Puri, Lokesh Kumar, and Arvind K. Bansal, "Trends in pharmaceutical taste-masking technologies: A patent review," *Recent Patents on Drug Delivery & Formulation*, Vol. 3, pages 26-39, (2009).

3. Daniel To, Jason Teckoe, and Ali Rajabi-Siahboomi, "Investigation of taste-masking performance of an aqueous ethylcellulose dispersion (Surelease) on acetaminophen granules," Poster session presented at the American Association of Pharmaceutical Scientists Annual Meeting, November 2013, San Antonio, TX.

4. Raxit Y. Mehta, Charles R. Cunningham, and Ali R. Rajabi-Siahboomi, "Evaluation of acetaminophen particle size and crystal morphology on taste-masking performance from coated granules and chewable tablets," Poster session presented at the Controlled Release Society Annual Meeting, July 2015, Edinburgh, Scotland.

5. AMBERLITE is a trademark of the Dow Chemical Company.

6. Edward F. Bouchard, Ira J. Friedman, and Roy J. Taylor, "Vitamin B12 products and preparation thereof," US patent no. 2,830,933, (1958).

7. Tussionex is a trademark of the UCB group of companies.

8. Delsym is a trademark of Reckitt Benckiser.

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