

Flavor Masking for Rx and OTC Drugs

Taste is one of the most important parameters in developing an Rx or OTC drug. Unpleasant, bitter-tasting components can make a product unpalatable which will impact patient compliance, marketability and, ultimately, product sales and profitability. If a product doesn't taste good, it's not going to sell well.



As part of our contract manufacturing services, PLD Pharma Services, a full-service CDMO, has developed expertise in flavor masking which we bring into play as we work with our customers to deliver products that offer efficacy in a palatable dosage form. PLD Pharma Services, which is a wholly-owned subsidiary of PL Developments (PLD), has more than 30 years of formulation experience. While PLD Pharma focuses on the development of oral solid and liquid dose Rx

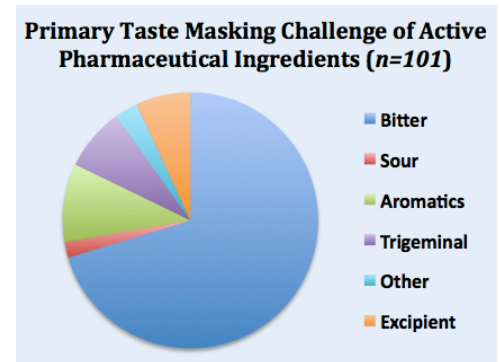
drugs, PL Developments manufacturers and packages a wide range of OTC pharmaceutical products and consumer healthcare goods.

In the past, pharmaceutical flavor masking generally centered on organoleptic techniques, which involve using “good” flavors to mask bad flavors, much like a chef in a kitchen operates. Whereas now, some of the dosage forms are migrating towards delivering drugs in the oral mucosal, which requires us to use techniques that typical flavor chemists wouldn't necessarily have at their disposal, but pharmaceutical companies would have in their toolbox. The skills that are necessary now that maybe weren't needed 10 or 15 years ago when there wasn't this big push to deliver drugs and be oral mucosa.

When considering techniques for taste masking, it's important to take a few things into consideration:.

- The degree of bitterness in the API.
- Knowledge of the properties of different excipients and how they can be used to mask the taste of the drugs.
- The dose load of the drug. When the dose is small it is easier to mask the taste. Higher doses are harder to mask.
- The shape of the drug. Irregularly shaped drugs can cause taste masking to be less effective depending on the technique used.

What's critical is that any taste-masking techniques are compatible with the drug formulation. For example, coated particles obtained after fluid-bed coating must be able to withstand the tablet compression process used for tablet manufacturing. Also important is how a product is stored or shipped. There was a company that was using chocolate for flavor masking. From that perspective it was very effective, but it was impossible to get the chocolate temperature stable; it needed to be refrigerated which made shipping and storage too challenging.



Source: Senopsyps

Flavor Masking Techniques

The simplest approach to flavor masking is using organoleptic methods: using “good” flavors – such as sweeteners and amino acids – to obscure the undesirable ones. It involves adding a combination of sweeteners (sucralose, aspartame, etc.) and flavors (citrus or mint, for example) to mask the unpleasant taste of low to moderately bitter actives. Many sweeteners are highly water soluble so they dissolve in saliva and coat the taste buds. Some formulations include a bitterness blocking agent that masks the bitter taste -- or the perception of bitter on the tongue -- such as adenosine monophosphate, lipoproteins, or phospholipids. These agents bind to the

receptor sites on the tongue that detect bitter flavors. With artificial sweeteners, one of the issues can be that they while the sweetener molecules activate sweetness receptors, they also engage receptors for bitterness, leaving an aftertaste. Some sweeteners are so overpowering that you need to taste mask them.

However, with actives that have especially strong or unpleasant tastes, or drugs delivered in the oral mucosal, it may be necessary to use more novel strategies, such as hot melt extrusion, microencapsulation, polymer coating, hot-melt extrusion, complexation, and spray-drying.

Let's look at some of these techniques:

Polymer coating: In this approach the API is coated with a polymer to provide a physical barrier over the drug particles that is insoluble in the mouth. That usually involves a hot melt extrusion process which sometimes involves combining the drug with polymers, melting them, and forming smaller particles.

Microencapsulation: This technique involves wrapping a membrane around a particle to block the taste.

Complexation to ion exchange resin: This involves dissolving the drug or drugs in a solution so the drug absorbs into an ion exchange resin that masks the taste.

Spray Drying: This is another technique where you embed the drug within another matrix, maybe a sugar crystal or a polymer, to mask the taste. We don't do spray drying in house, but we have partners that we can work with if it's needed.

These are not necessarily new techniques but are new to the flavor masking arena and became necessary when we started manufacturing orally disintegrating or orally dissolving tablets (ODTs) – specifically some of the antihistamines such as Zyrtec and Claritin, which are designed to dissolve on the tongue rather than be swallowed whole.



We also started looking at different flavor masking techniques and novel dosage forms as PLD started to get more involved with pediatric medications, which are challenging to make palatable because children are more sensitive to flavors than adults, especially bitter tastes. Anyone who has children knows it's almost impossible to formulate a liquid medication that children find acceptable and it's even more difficult to get them to take solid dosage forms. So, for pediatric Rx and OTC drugs, we have been investigating gummies, which have a nice texture and mouthfeel and could improve compliance.



Of course, there are challenges associated with formulating gummies, that need to be addressed by scientists who have experience both with the APIs and the dosage form. For example, some of the ingredients in flavorings can act like plasticizers and could cause the gummy to not set up properly so you need to be very careful about which flavorings you use and how much. So far, dealing with the “normal” flavors (such as strawberry, mixed berry, grape, cherry and lemon-lime), we’ve not experienced any issues.

Finding the Right Balance

Like cooking, flavor masking requires a lot of trial and error to find the right balance. Our R&D lab has a lot of experience creating formulation recipes but, in every case, a lot depends on how the flavors meld together. We all know how unpleasant it can be if you put too much salt in a recipe, and the same thing can happen if you put too much sugar or overdo the sour notes.

With most of the actives that we use in formulations, the problem is they're bitter. One of the most popular flavors to mask bitterness are sour notes – citrus notes. Think about the Jolly Rancher flavors. Those are phenomenal across the board and can be a good reference point when developing pediatric drugs.

The success of flavor masking has a lot to do with the dosage. If, for example, you want to produce an OTC ibuprofen gummy, the dose is 200 milligrams, which has a strong bitter flavor. Trying to mask that is proving to be difficult.

While sweeteners are one of the most common ingredients used in flavor masking, there are times when a formulation becomes too sweet, which is also a problem. One of the issues is that when using artificial sweeteners, their sweetening capabilities are often 200 times more powerful than sugar. Why not use real sugar? There’s been a movement to remove sugar from OTC and Rx drugs to accommodate consumers who are trying to lose weight or control their blood sugar levels and artificial sweeteners are typically more stable than sugar, which can break down over time and change the taste of a formulation. However, artificial sweeteners also activate the receptors on the tongue for bitterness, which can leave an unpleasant aftertaste, so that must also be managed.

Flavor Masking Improves Compliance and Market Appeal

Up until recently, the pharmaceutical industry didn’t put a lot of emphasis on flavoring, but as companies realize that a good tasting product offers them a competitive advantage and improves compliance, pharma companies are taking the aspect of flavor more seriously and they are looking for CDMOs that have experience with this element of formulation.

One example of how much flavor masking can boost a product’s market appeal and compliance,



is the Rogue portfolio of tobacco products, developed by PL Developments, as it was the flavors that really made that portfolio take off. Competitive products either didn't have enough flavor, had a chemical taste, or a delayed response. When we formulated the Rogue Nicotine products, we were able to create a sharper, more pronounced flavor that lasted – so much so it seems like you have a breath mint in your mouth. That product line has outperformed its competitors and developed a strong following.

Also critical is that the formulating team have experience with FDA approvals because as taste masking is taking a more prominent feature, and companies are using stronger flavors, regulatory concerns are also emerging. There's a regulatory concept called GRAS -- Generally Recognized as Safe – that's used in OTC and candy flavorings. But with Rx drugs, the FDA is scrutinizing the amounts of flavors and which flavors are being used, evaluating safety and efficacy. That makes our job even more tricky because we must evaluate the safety of the flavorings, how it might impact efficacy, and also consider that if a drug tastes too good, some people might take too much of it.

To create a strawberry flavor, for example, requires a mixture of chemicals and flavonoids. It's important to understand what levels of these ingredients can be added before there is a problem. You need to understand what amount of specific ingredients can be added before it creates a problem. This is especially important if you're using a gummy as a delivery platform because people might suck on them as opposed to chewing them. There are some flavorings – such as wintergreen, which is a staple in the tobacco industry -- that are incredibly strong. Wintergreen oil is so strong that you could literally strip paint from your walls with it so if you were to put that in a dosage form that you put in your mouth, maybe multiple times a day, it could cause blisters.



Mouthfeel Vs. Flavor Masking?

Mouthfeel is different from taste, although they are related. Mouthfeel refers to the physical sensations in the mouth caused by a food product or a drink. For example, PLD recently developed a line of mouthwashes, which use flavonoid terpenes such as pine and eucalyptus. In that example, it's the terpenes that do all the work but it has a very harsh mouthfeel. To make the formulation feel "smoother", we lowered the amount of alcohol, which made it taste medicinal, and added sorbitol, a sugar alcohol, to act as a smoothing agent and cuts the hardness that exists from the ingredients.

What to Look for in a Development Partner

When developing a new drug, the increasing emphasis on flavor masking means that there are a few more boxes to check when looking for a development partner or CDMO. Flavor masking is difficult, so you need to find an organization that has:

- Knowledge of the properties of different excipients and how they can be used to mask the taste of drugs.
- Experience with a variety of taste masking techniques, such as using sweeteners, flavors, and coating agents.
- Ability to design and conduct taste tests to evaluate the effectiveness of different formulations.
- Knowledge of Good Manufacturing Practices (GMP) and how to comply with them.
- Strong communication and interpersonal skills.
- The ability to work independently and as part of a team.

At PLD we're not experts, but we are very resourceful. We are seasoned professionals who understand APIs and understand that flavoring is an important part of delivery systems. We have a knowledge base in-house with an experienced team and the capabilities to perform a wide range of flavor masking techniques. Ninety percent of the battle is understanding what you don't know and getting help in those areas, which is why we have established partnerships with flavor houses, to provide skills that we might not currently offer – and we learn a lot from our customers who might have tried different techniques in the past.



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