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White Paper

Taste Optimization in Solid Dose: A Human Sensory Panel Study

Introduction

Rejection of bitter medicine is a human survival mechanism: Natural poisons often taste bitter. Ironically, beneficial substances can also be unpalatable. Formulating remedies to be more appetizing is crucial to patient compliance, particularly in the pediatric and growing geriatric populations. Palatability can also factor greatly in brand selection, especially in the case of over-the-counter medications. For these reasons, in pharmaceuticals, taste matters.

But what is the current thinking on taste? Small protuberances on the tongue, papillae, house the taste buds with their taste receptors. Chemical stimulation of the taste receptors via surface proteins or ion channels cause electrical changes within the cells that trigger neurotransmissions to the brain.[1] These signals register as sweet, salty, sour, bitter or umami (savory). Olfactory stimuli, which are transduced via the olfactory epithelium within the nasal cavity, also contribute to the sensation. Recent studies have even indicated that people, irrespective of culture, consistently associate certain colors with particular tastes.[2]

In the food and pharmaceutical industries, taste is sometimes evaluated using electronic tongues — sensory arrays able to evaluate complex mixtures via sensor membranes and electrochemical techniques.[3] While this method is convenient and consistent, it does not provide a holistic picture of taste as it neglects factors such as olfaction and mouth feel.

Despite our understanding of some of the underlying physiology, taste is still a highly subjective attribute. One thing people generally agree upon, however, is that sweet is good. For this reason, the first choice for making a pharmaceutical formulation more acceptable is often to add taste-modifying ingredients and/or sweeteners. Additionally, simply adding a sweet component necessitates no special equipment nor extra production steps. Other available taste-masking methods, such as coating the API, require much more effort and expense and may reduce bioavailability.

However, a pharmaceutical formulation is not only made up of the API and taste modifiers. All solid dosage formulations contain fillers, which typically comprise a high percentage of the formulation. Fillers are inert bulking agents with mechanical properties — such as high flowability, good compressibility or low moisture absorption — that offer advantages such as improved uniformity or ease of manufacturing. Since sugar and sugar alcohols are starches, these fillers are somewhat sweet and the sugar alcohols — xylitol and sorbitol, and, to a lesser extent, mannitol — also produce a pleasant, cooling effect created by endothermic dissolution.

Taste and palatability are important as they directly affect patient perception and compliance.

Hence, the study discussed here examines the taste-optimization efficacy of several common solid-dose fillers on their own and in combination with a variety of sweeteners.

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Overall method

In a randomized, blinded study, an eight-person professional sensory panel evaluated the taste-modification properties of seven commonly used sugars, starch and sugar alcohol fillers alone and in combination with three separate artificial sweeteners. Each test combination was evaluated for its ability to mask the bitter taste of quinine. As per Quantitative Descriptive Analysis® (QDA) methodology[4], testers were given 500 mg doses of a test mixture and asked to fill out a detailed, sensory evaluation standard questionnaire on multiple aspects of the taste sensation. Bitterness was judged overall and also according to speed of onset and degree of aftertaste. Before progressing to the next sample, the professional testers rinsed and neutralized their mouths.

Chemicals used are listed in Table 1.

Table 1:

Fillers tested include a range of sugars, sugar alcohols and starches. Three artificial sweeteners were also tested. Quinine was the model bitter API.

Material	Supplier	Chemical type
Fillers		
Lactose monohydrate	Merck KGaA, Darmstadt, Germany	Sugar
D-Fructose	Merck KGaA, Darmstadt, Germany	Sugar
MCC (Type 102)	JRS Pharma, Ulm, Germany	Refined wood pulp
Mannitol (Parteck® M 200 excipient)	Merck KGaA, Darmstadt, Germany	Sugar alcohol
Sorbitol (Parteck® SI 150 excipient)	Merck KGaA, Darmstadt, Germany	Sugar alcohol
Xylitol	Roquette, Lestrem, France	Sugar alcohol
Maltodextrin (Linecaps 17)	Roquette, Lestrem, France	Pea starch
Artificial Sweeteners		
Sucralose	Merck KGaA, Darmstadt, Germany	Sweetener (300x sucrose)
Sodium saccharin	Merck KGaA, Darmstadt, Germany	Sweetener (300–1000x sucrose)
Fine granular aspartame/ 60–100 mesh	Anhui Elite Industrial Co., Ltd., Hefei, China	Sweetener (200x sucrose)
Model API		
Quinine HCl	Chemische Werke Hommel GmbH & Co. KG, Waltrop, Germany	Alkaloid from *Cinchona* bark

Round 1: How well can the fillers, alone, mask bitterness?

In the first round of evaluation, each filler was mixed with quinine as a model bitter API (0.06 %) and tested without additional sweeteners, since these fillers all offer some intrinsic sweetness. Two maltodextrin/xylitol combinations were also tested. The results are shown in Table 2, with a better experience reflected by a lower score, on a scale from 1 to 7.

Descriptor	Lactose	Fructose	Microcrist. Cellulose	Mannitol	Sorbitol	Xylitol	Malto-dextrin	Maltodextrin plus 25 % Xylitol	Maltodextrin plus 50 % Xylitol
Sweetness	5.2	2.4	6.3	3.9	2.8	2.7	4.7	3.8	3.1
Onset of bitterness	3.5	2.5	3.2	2.4	2.1	2	3	2.6	1.9
Grittiness of granulate	2.6	4.7	1.8	2.7	1.8	0.5	4.8	4.3	4.5
Dissolution of granulate	3.3	2	6.3	2.5	1.1	0.7	4.5	3.9	2.8
Clumping	1.1	0.7	5.8	0.9	0.3	0.1	5	3.6	2.5
Overall bitterness	4.3	3.2	4.5	3.1	2.9	3.1	4.2	3.7	3.2
Stickiness	2.1	1.7	6.1	1.4	0.5	0.4	5.7	4.5	3.4
Cooling effect	7	6.4	7	5.9	2.4	3.5	7	6.1	5.6
Bitter aftertaste	4.2	3.6	4.3	2.9	3.5	3.5	3.6	3.8	3.4
Mouth-filling	3.4	2.7	4.6	2.5	2.8	2.9	3.2	3.2	2.9
Overall grading	**36.7**	**29.9**	**49.9**	**28.2**	**20.2**	**19.4**	**45.7**	**39.5**	**33.3**

Table 2:

Taste evaluation of various fillers in combination with quinine as a model bitter API. The lower the value on a scale of 1-7, the better the impression.

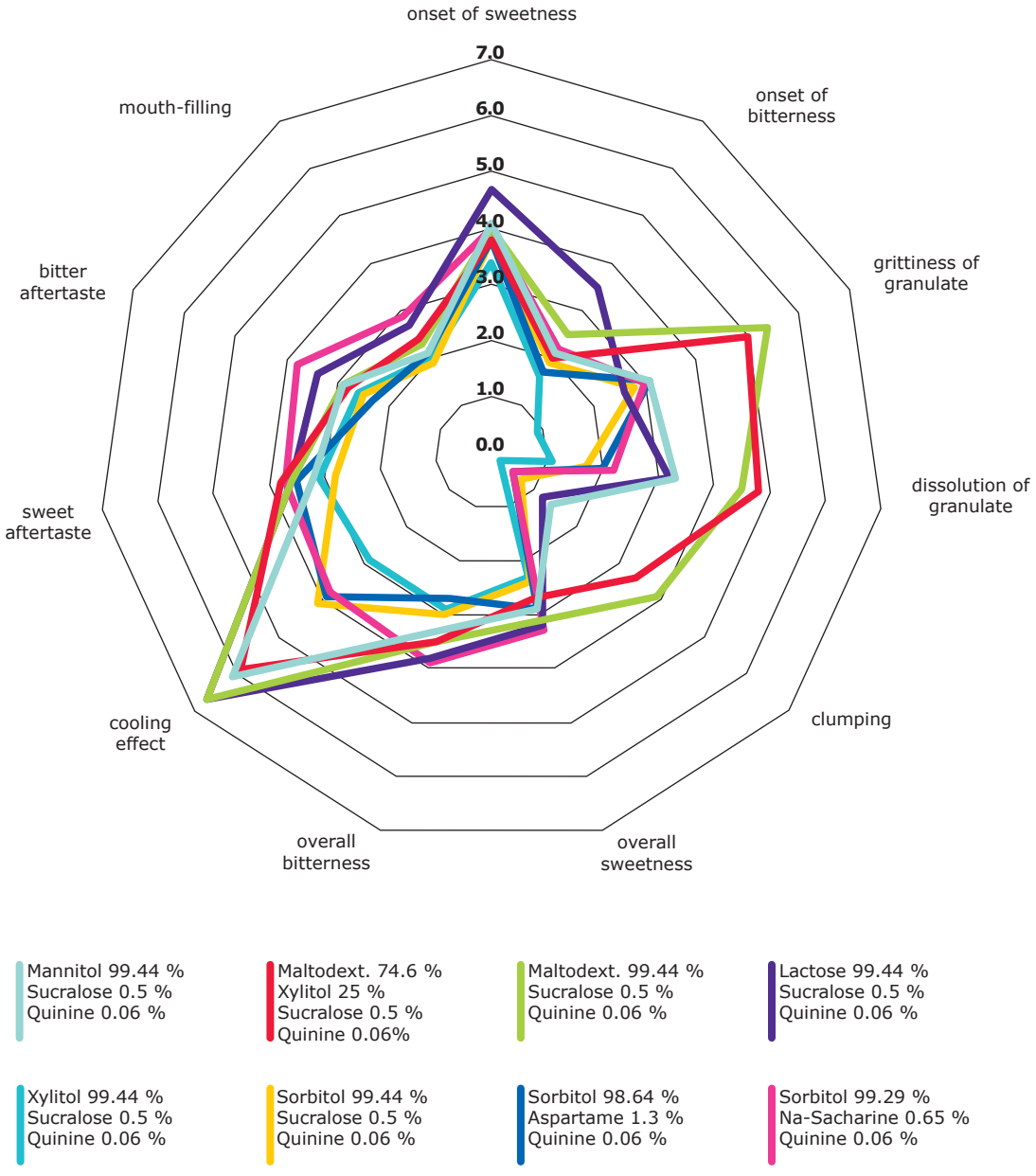
The overall ratings for the sugar alcohols, especially sorbitol and xylitol, were the most favorable. Starch fillers microcrystalline cellulose (MCC) and maltodextrin received the least favorable ratings, largely due to textural issues such as poor dissolution, clumping and stickiness. Combination with xylitol improved maltodextrin, but not enough to make it perform as well as sorbitol, xylitol or mannitol.

Round 2: What happens if artificial sweeteners are added?

Since none of the fillers were able to overcome the model API's bitterness, new combinations incorporating sucralose were tested. Results for lactose, the sugar alcohols and maltodextrin with and without xylitol are shown on the spider graph, Figure 1. Xylitol and sorbitol hug the center most closely. Both maltodextrin samples still have texture issues. Lactose demonstrates a delay in the onset of sweetness, and none of these, including mannitol, can compete with the cooling effects of sorbitol and xylitol.

Figure 1:

Taste evaluations of various fillers mixed with quinine and sweeteners. The lower the value and the smaller the area enclosed by the curve, the better the impression.



Round 3: Which artificial sweetener is the best?

To determine which artificial sweetener was best able to cover the bitter API, sucralose, aspartame and sodium saccharin (at concentrations adjusted to ensure comparable sweetening power) were tested in combination with sorbitol. Sorbitol was selected because it was one of the high-performing fillers and is more commonly used in the pharmaceutical industry than xylitol. The results in Figure 1 show that all three combinations perform well. However, in this representation, it's difficult to identify the differences in performance among the three artificial sweeteners.

For better differentiation, this test was expanded to include multiple concentrations of each of the sweeteners. Results for onset of bitterness, overall bitterness and bitter aftertaste are shown in Figure 2.

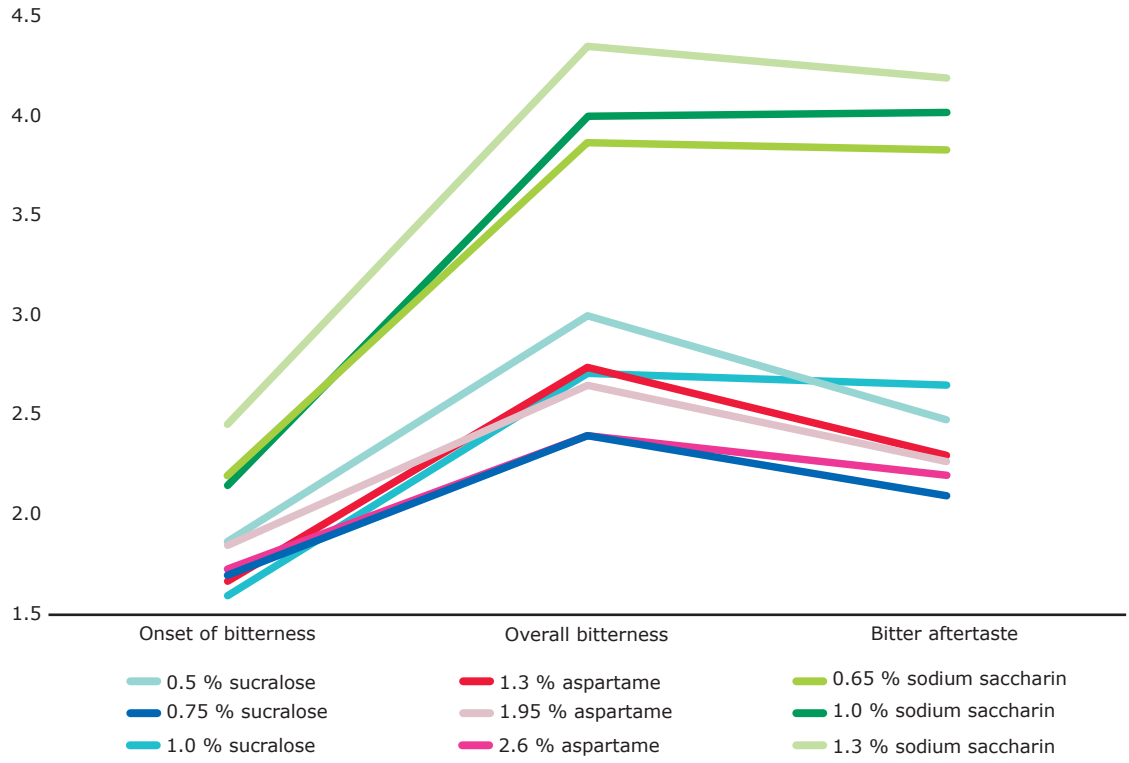


Figure 2:

Professional sensory panelist evaluation of the development of bitterness over time. Test samples included three sweeteners at multiple concentrations, combined with the filler sorbitol and the bitter model API. The lower the value the better the impression.

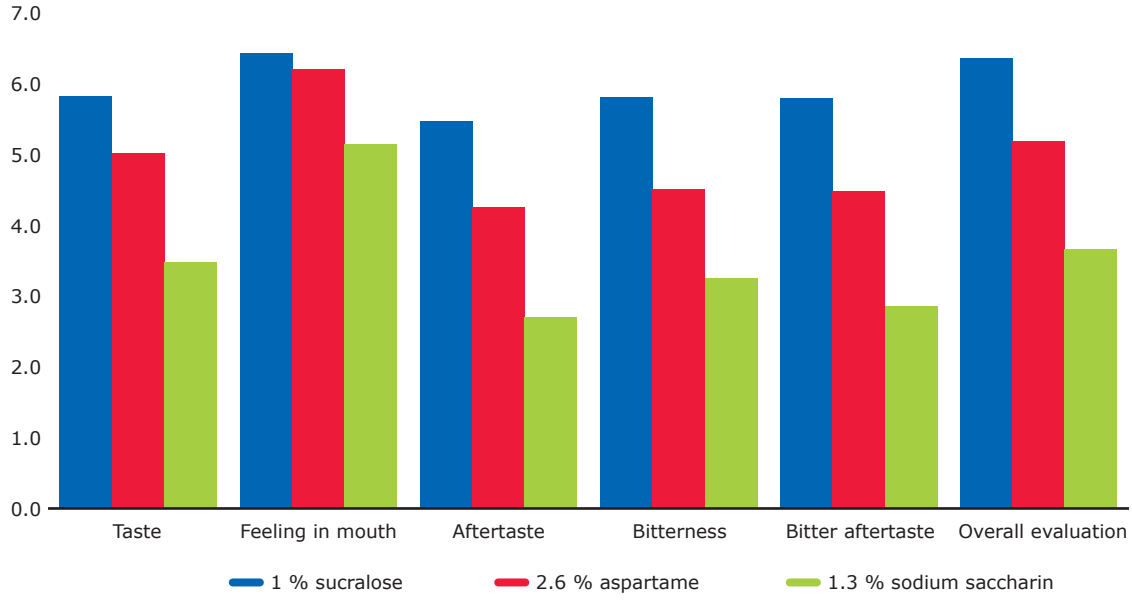
While the mechanism for aftertaste is poorly understood, some artificial sweeteners are known for their bitter aftertastes, as demonstrated here by saccharin. For sucralose, 0.75% seems to represent a sweet spot, with similar performance by 2.6% aspartame.

Round 4: How do untrained people rate the sweeteners?

Finally, in the fourth test cycle, 57 untrained tasters were asked to evaluate how pleasant they found the taste of the three sweeteners, each in combination with sorbitol (see Fig. 3).

Figure 3:

Taste evaluation of formulations with 1, 2.6 or 1.3% sweetener with 0.06% quinine and sorbitol ad 100% by a 57-person statistical untrained consumer test panel. In this evaluation, higher values indicate better impressions.



Discussion

The bitter taste of some medications is normally the product of direct chemical interaction between the API and the taste buds, and it is this response that has drawn the most attention from formulators. Electronic tongue evaluation has shown that complexing bitter APIs with maltodextrin can mask their taste, albeit weakly.[5] However, this study clearly demonstrates that the unpleasant taste sensations caused by insoluble excipients in the starches tested override this effect. For this reason, maltodextrin and MCC, which are broadly applied in solid oral formulations, should be rejected as fillers in taste-sensitive applications.

Palatability may be a more apt term than taste to describe the complete sensory experience that must be considered when evaluating medications. As this study shows, taste buds are not the only factor, with dissolution properties and the medication's mouth feel also playing important roles. A cooling effect makes formulations more pleasant, while insoluble particles make them less pleasant. Together with sweet, sour, bitter, salty and savory tastes, these factors form a complex multiparameter array that can only be effectively evaluated by well-trained human testers.

Sweetening is still the most efficient way to counteract a bitter taste, especially in synergy with a cooling effect created by endothermic dissolution, as in the case of the sugar alcohols. The sweetness of fillers, however, is not sufficient to mask the bitterness of APIs, necessitating the addition of high-intensity sweeteners. For this purpose, the panelists preferred sucralose. Note that some sweeteners were actually counterproductive in that they intensified the bitter aftertaste of the simulated API.

Conclusion

A combination of smoothly dissolving sorbitol or xylitol with sucralose as a sweetener was found to be the most favorable excipient combination for optimizing the taste of a formulation containing a bitter API.

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