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A Taste Receptor Blocker for Oral Hygiene Compositions

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Abstract

A hydrogenated, ethoxylated glycol ester reduces the harsh taste or burn sensation ordinarily imparted by the eucalyptol and the astringency ordinarily caused by the zinc salt in oral hygiene compositions.

It has long been the goal of formulators and flavorists to cover or mask unpleasant tastes arising from active ingredients incorporated in oral hygiene products. The positive effects of these actives were often overpowered by the negative taste effects experienced by the user.

Zinc, for example, while possessing excellent germicidal activity and the ability to freshen breath, has a strong metallic taste accompanied by astringency (a drying of the mouth). Thymol provides antimicrobial activity but it is associated with a harsh taste or burn sensation.

Heretofore, attempts were made to cover these negative attributes by flavor variations, combinations of different sweeteners, and use of other possible masking agents. However, these attempts either failed or brought negatives of their own.

This article reports on a different technique: a method to block the taste receptors with a hydrogenated, ethoxylated glycol ester. The taste receptor blocker was tested by flavor panels and antimicrobial challenge. Then it was formulated with a flavor system into a mouth rinse that was also tested by a flavor panel.

Masking Unpleasant Tastes

Flavor in an oral hygiene product plays two important roles: it provides a refreshing taste and feel in the mouth and it masks the natural flavors of the raw materials in the product.[1]

The oral cavity is filled with taste receptors that respond to different sensations: sweet, sour, salty, bitter and umami (the taste of certain amino acids). For instance, alcohol and certain essential oils have a biting, burning taste. Formulators in the past have used variations of flavors, combinations of sweeteners and other techniques to mask unpleasant tastes.

One example is the use of anethol with a polyalcohol to reduce the burning effects of thymol.[2]

Another example is the attempt to mask the metallic taste of zinc by using a combination of sweeteners such as saccharin and ammonium glycyrrizinate (a licorice root extract).[a] It was found that zinc has a profile of effect in the oral cavity: the astringency and metallic taste build over time and occur mainly in the back of the mouth. Saccharin's sweetness is immediate while that of ammonium glycyrrizinate builds with time. Like all anise-based products, it affects the back of the oral cavity. Therefore, some early attempts to mask zinc used anethol and the saccharin-ammonium glycyrrizinate combination that had a directional improvement, meaning that it reduced the burn somewhat but not completely.

The work reported in this article was initially centered around masking the burn associated with a commercial antiseptic mouthwash (Product A). A flavor brief requested the development of a new mouthwash (Product C) whose taste was as acceptable as that of a commercial non-antiseptic mouth rinse (Product B).

In order to properly cover the burning sensation, it was necessary to identify the agent or agents responsible for the burn. At least one source[3] suggested that thymol was the causative agent together with the alcohol, but that needed confirmation.

Product A's active ingredients were eucalyptol, thymol, menthol and methyl salicylate. In our lab we individually dissolved the formula amount of each active in alcohol and then prepared individual mouth rinses using

[a] *Magnasweet is a trade name of MacAndrews & Forbes, Camden, New Jersey, USA*

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the formulation amounts of the remaining excipients. Evaluation of the samples by an in-house expert panel revealed that the eucalyptol and not the thymol was responsible for the burning.

Having identified the agent responsible for the burn, we began to formulate a flavor containing a citrus note (lemon or lime), which has a tendency to smooth out harsh qualities of other oils. We increased the level of sorbitol used in the base formulation, which had earlier been shown to reduce the burning. Finally, to optimize the entire system, we combined the saccharin with ammonium glycyrrizinate.[b] This completed system – flavor, sorbitol and combined sweeteners – now matched the timing profile of the burn in the mouth and had a strong directional improvement for reducing the burn (Formula 1).

The Taste Receptor Blocker

Researchers at Johns Hopkins University discovered a method for identifying substances that stimulate or block salty taste perception.[4] This method used amiloride hydrochloride ($C_6H_8ClN_7O \cdot HCl \cdot 2H_2O$), a compound that has been shown to sensitize the sodium channel of the taste buds for salty taste. We therefore reasoned that if we could identify a material that worked the way amiloride works with salt receptors, we could block the receptors from perceiving the negative attributes of certain actives. By rendering the taste receptors incapable of recognizing the negative stimuli, we could effectively mask the negative attributes. To accomplish this we would need a material that would in effect "coat" the area with a film-like covering.

The use of a fat or an oil was immediately suggested. The fat triglycerol monooleate[c] did block the burn, but it rendered the finished product cloudy and opaque, and therefore was unacceptable. Another fat, caprylic/capric triglyceride,[d] also blocked the burn but produced a cloudy mouth rinse.

Although both experiments failed, they proved that the hypothesis was sound: fat-like substances prevent the taste receptors from perceiving the burn. However, we needed a material that would produce a clear product. Subsequent experiments determined that one satisfactory material is PEG-60 hydrogenated castor oil,[e] a solubilizing surfactant that in nearly all flavor systems produces a clear solution.

PEG-60 hydrogenated castor oil is a hydrogenated, ethoxylated glycol ester. It has the mouth-feel characteristic of a fat but a much higher degree of solubility and hence improved clarity in oral hygiene compositions.

PEG-60 hydrogenated castor oil is produced by the ethoxylation of hydrogenated castor oil. When hydrogenated castor oil combines with ethylene oxide during ethoxylation, the hydrogen bonding to the oxygen makes the polyethylene end of the molecule more water-soluble. As the ethoxylation number decreases, the fat characteristic of the molecule and hence its efficiency in coating and blocking the taste receptors increase, but the solubility usually decreases, thereby decreasing clarity. If the fat characteristics of the compound are too great, solubility in the mouth rinse is adversely affected, which results in an undesirable cloudiness for the product. Accordingly, the taste receptor blocker should be selected so as to strike the proper balance between coating efficacy on the one hand and clarity on the other.

The ethoxylated compounds are designated[5] as PEG-XX, where XX is a numeral indicating the degree of ethoxylation in terms of the number of moles of ethylene oxide added. Ethoxylation numbers in the range of from 35 to 60 have been found to provide the best results in terms of good solubility and good clarity.

The amount of taste receptor blocker incorporated in the composition will depend upon the amount of eucalyptol contained in the composition as well as the degree of reduction desired in the burning sensation imparted by the eucalyptol.

In an antiseptic mouthwash, eucalyptol is typically present in amounts ranging from 0.07 to 0.11% by weight. For such typical concentrations, the amount of hydrogenated, ethoxylated glycerol ester may be as low as 0.5% by weight in order to provide a good result in terms of reducing burning sensation. For such typical eucalyptol concentra-

[b] *Magnasweet 120*

Formula 1. Antiseptic mouthwash with citrus flavor and masking by sweeteners (Product C)

Alcohol base (thymol, eucalyptol, menthol and methyl salicylate)	19.50% wt
Flavor	0.05
Anethole	0.02
Sorbitol, 70%	30.00
Saccharin	0.15
Ammonium glycyrrizinate (Magnasweet 120, MacAndrews & Forbes)	0.15
Water (*aqua*), deionized	50.13
	100.00

[c] *Mazol PGO 31K, BASF Corp, Mount Olive, New Jersey, USA*
[d] *Miglyol, CONDEA Chem GmbH, Marl, Germany*
[e] *Cremophor CO-60, BASF AG, Ludwigshafen, Germany*

tions, preferred amounts of the receptor blockers are from 0.5 to 5.0% by weight. The most preferred taste receptor blocker amount is about 2.0% by weight. These levels would also be appropriate in toothpaste.

The preferred amounts have been found to substantially eliminate the burning sensation without detracting from the clarity of the oral hygiene composition or adversely affecting its flavor.

Experimental Procedures

This newly formulated mouth rinse (Formula 2) containing the taste receptor blocker successfully blocked the burning of eucalyptol and remained a clear solution, but it also needed to satisfy two tests: an expert flavor panel evaluation and a test of its antimicrobial activity.

Flavor panel evaluation: The flavor evaluation used six trained panelists who evaluated the burn sensation of three products at three time points. The products were the experimental product (CC, Formula 2), the commercial antiseptic brand (A) and the commercial non-antiseptic brand (B). They were evaluated during swishing (20 mL of product in mouth for 30 seconds), immediately after expectorating and 90 seconds after expectorating. The panelists were trained to use a six-point burning intensity scale in which 6 represents intense burning (as in the taste of Product A) and zero represents no burning (as in the taste of water).

Each panelist tasted each product three times with two hours between tastings. The 18 evaluations for each data point were averaged and analyzed using the Student T-test at various confidence levels.

Antimicrobial challenge: An in vitro antimicrobial challenge against *Pseudomonas aeruginosa* was conducted by Collaborative Microbiology Labs of Stony Brook, New York. To pass the test, an active antimcrobial ingredient must kill all test organisms, in the presence and in the absence of serum, within two minutes.

Once again, our Product CC was the test sample. The controls were Products A and Product D, which was another commercial antiseptic mouthwash from the same company. The test organism was an overnight culture of *Pseudomonas aeruginosa*, ATCC 9027.

One mL of the test culture and 9 mL of the product were mixed rapidly. At 1 and 2 minutes, 0.1 mL of the mixture was removed and inoculated into tubes containing 9.9 mL of Lentheen Broth, the inactivating medium.

The product and the test culture were brought to temperature equilibrium in a water bath at 37°C and held at this temperature throughout the test.

Tubes were inoculated at 37°C for 48 hours and observed for growth. If no apparent growth was seen after 48 hours, the entire contents of the tubes were transferred to 90 mL of inactivating medium to further dilute any carry-over of active ingredient.

If upon further incubation for one week at 37°C no growth was detectable, the test organisms were considered to be killed by the product or its ingredients.

Formula 2. Antiseptic mouthwash with taste receptor blocker, citrus flavor and masking by sweeteners (Product CC)

Alcohol base (thymol, eucalyptol, menthol and methyl salicylate)	19.50% wt
Flavor	0.05
PEG-40 hydrogenated castor oil PCA isostearate (Cremophor CO-40, BASF AG)	2.00
Sorbitol, 70%	15.00
Saccharin	0.15
Ammonium glycyrrizinate (Magnasweet 120, MacAndrews & Forbes)	0.20
Water (*aqua*), deionized	63.10
	100.00

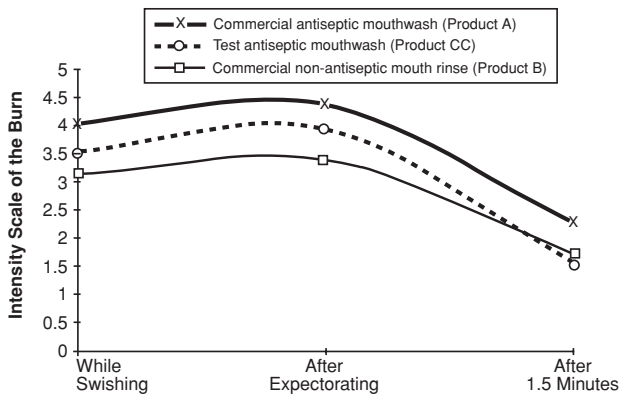

Figure 1. Flavor panel evaluation of the burn sensation in the taste of three oral hygiene formulations

Viability controls were included by mixing 1 mL of test culture with 9 mL of BHI (brain heart infusion) and adding 0.1 mL of this mixture to inactivating medium, and then incubating at 37°C.

Each product was also tested in the presence of biological fluids: 2 mL of BFS (bovine fetal serum) heat activated was added to 2 mL of the test organism. Two mL of the mixture was added to 8 mL of the product, mixed and tested.

Results

The results indicated that the test Product CC maintained the germicidal qualities of Products A and D.

Flavor panel evaluation: Results of the flavor panel's evaluation of the burn sensation are shown in Figure 1. The Student T-test showed that Product CC delivered a significant reduction of burn while swishing, immediately after expectorating and 90 seconds after expectorating, with confi-

dence levels of 85%, 80% and 95%, respectively.

During swishing, the taste receptor blocker is able to suppress the burn from Product CC, compared to the burn from Product A. After expectorating, both the negative taste profile and the mouthfeel of the active ingredients are suppressed. Panelists reported that the after-taste of Product CC showed less burning than either of the other products.

Antimicrobial challenge: Table 1 shows the results of the antimicrobial challenge. Product CC showed no growth of *P. aeruginosa*. The test samples appear to be effective against this microbe.

Discussion

Zinc salts and astringency: In addition to eucalyptol, other additives frequently incorporated into oral hygiene compositions for their antimicrobial properties are zinc salts. The zinc salts have also been used in commercial products for their tartar control properties.

Another advantage of using a taste receptor blocker is that it also has the effect of reducing or eliminating the astringency ordinarily imparted by the presence of zinc salts. Typical zinc salts, which are incorporated into mouthwashes and dentrifices, are zinc chloride, zinc citrate, zinc acetate, zinc lactate, zinc salicylate and zinc sulfate.

The amount of zinc salt present in a mouthwash is typically 0.01-1% by weight, and more typically 0.02-0.5% by weight in terms of zinc ion based on the total amount of the composition. For such typical amounts, the amounts of taste receptor blocker described earlier for reducing the burning sensation of eucalyptol are also effective for substantially reducing or eliminating the astringency imparted by the zinc.

A three-component flavor system: The taste receptor blocker is most preferably used in combination with a flavor system containing at least one spice note, at least one sweet note and at least one fruity note. It has been found that the spice note contributes towards reducing the astringency ordinarily imparted by the zinc. The sweet note has been found to be effective in enhancing the sweetness of the system as well as reducing adverse effects (such as bitterness) of the eucalyptol and zinc antimicrobial actives. The fruity note also helps to reduce the residual effects of the actives.

This three-component flavor system provides a sensory change in the mouth, which, in combination with the taste receptor blocker, completely eliminates the burning sensation and astringency normally associated with eucalyptol- and zinc-containing oral hygiene compositions.

The spice note used in the flavor system may be selected from spices that are commonly known, preferably ginger, clove, anise, cinnamon, nutmeg or mixtures thereof. A preferred sweet note is vanillin, especially ethyl vanillin. The fruity

Table 1. Antimicrobial challenge test (*Pseudomonas aeruginosa*) on experimental mouthwash Product CC, and two commercial antiseptic mouthwashes (Product A and Product D)

Sample	Time (min)	Growth or No Growth	ID
Test Product CC (at 2 days)	1	G	GP rods
	2	NG	
Test Product CC (at 7 days)	1	NG	
	2	NG	
Commercial Product A (at 2 days)	1	NG	
	2	G	GP rods
Commercial Product A (at 7 days)	1	NG	
	2	NG	
Commercial Product D (at 2 days)	1	NG	
	2	NG	
Commercial Product D (at 7 days)	1	NG	
	2	NG	
Viability control	1	G	GN rods *(P.a.)*
	2	G	GN rods *(P.a.)*
Test Product CC + BFS	1	G	GN rods *(P.a.)*
	2	NG	
Commercial Product A + BFS	1	NG	
	2	NG	
Commercial Product D + BFS	1	NG	
	2	NG	

GP = Gram-positive
GN = Gram-negative
BFS = Bovine Fetal Serum

Formula 3. Flavor system containing a spice, sweetener and fruity note

Flavor component name	Formula parts
Anethole	370
Carvone laevo	100
Cassia syn. (Noville)	100
Estragole	15
Ethyl vanillin	10
Ginger oil	30
Ginger oleoresin	25
Lemon 10-Fold	20
Linalool	5
Raspberry spirit concentrate (Noville)	25
Spearmint terpeneless	300

Formula 4. Antiseptic mouthwash with taste receptor blocker, preferred three-component flavor system and masking by sweeteners (Product CCC)

Alcohol (ethanol and essential oils thymol and eucalyptol)	19.00% wt
Poloxomer 407 (Pluracare/Pluronic F-127, BASF Corp) (surfactant)	0.05
Flavor system (from Formula 3)	0.15
PEG-60 Hydrogenated castor oil (Cremophor-60, BASF)	2.00
Water (*aqua*), deionized	58.61
Zinc chloride	0.09
Sorbitol, 70%	20.00
Sodium saccharin	0.10
	100.00

note may also be selected from among those known in the flavoring art, with raspberry and lemon oil being preferred. One particularly preferred flavor system for use with PEG-60 hydrogenated castor oil is shown in Formula 3.

For maximum effectiveness, the flavor system would typically be used in amounts from 0.05 to 0.25% by weight based on the total oral hygiene composition, depending upon the flavor one wanted to impart to the composition. Preferred amounts are from 0.1 to 0.2% by weight, with 0.15% as the most preferred amount.

The new mouth rinse system (Product CCC) with the three-component flavor system is shown in Formula 4. Products A, B and CCC were comparison tested by a flavor

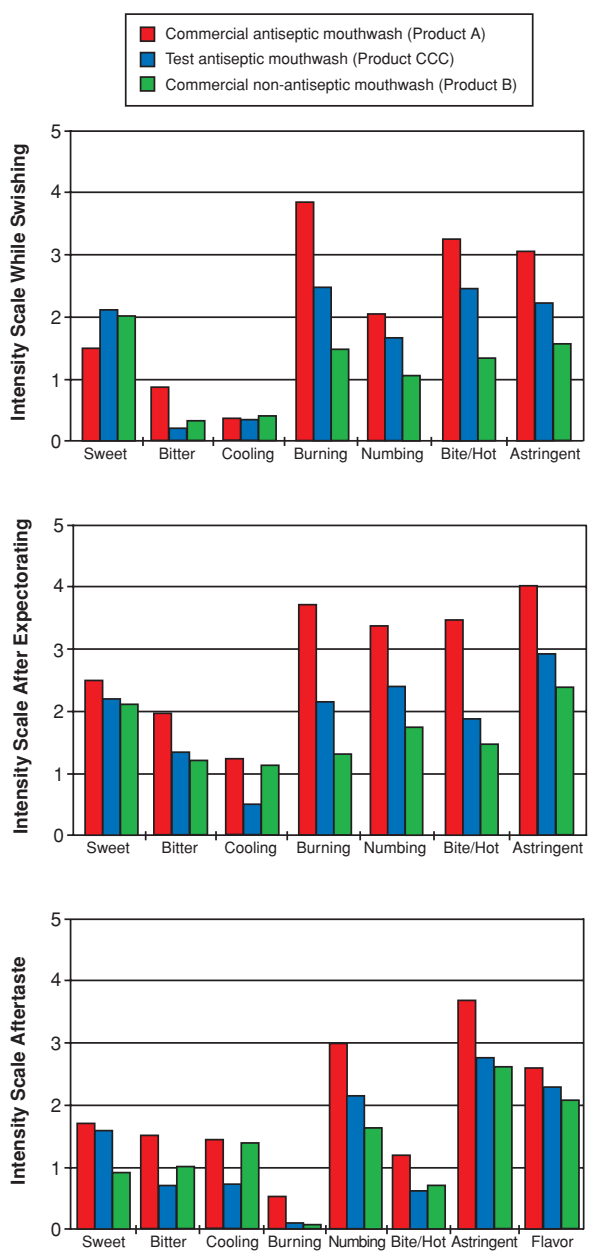

Figure 2. Flavor panel evaluation of the taste of three antiseptic mouthwash products while swishing (top), after expectorating (middle) and after-taste at 90 sec (below)

panel at three time points: while swishing, after expectorating and for aftertaste at 90 seconds. As shown in Figure 2, Product CCC blocked both the burn of the eucalyptol and the astringency of the zinc, demonstrating overall improvement using the experimental system.

Conclusion

We have identified a hydrogenated, ethoxylated glycol ester that functions as a taste receptor blocker in oral hygiene compositions and can be used alone with different flavors and/or in combination with a specific flavor to successfully mask the burn of eucalyptol and the astringency of zinc.

This blocker showed good results in a mouth rinse system. It also can be used in toothpaste and gels. A patent has been issued[6] protecting the formulas given here, the use of Cremophor and the use of the flavor. Licensing agreements are possible. The protected ideas presented here are not currently being used in any marketed products.

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