

TASTE-MASKING ACTIVES

Masking Bitter Taste of Pharmaceutical Actives

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INTRODUCTION

There are numerous pharmaceutical and OTC preparations that contain actives, which are bitter in taste. With respect to OTC preparations, such as cough and cold syrups, the bitterness of the preparation leads to lack of patient compliance. Currently, companies are developing dissolvable films as alternative dosing mechanisms for drug actives for patients who are unable to use the traditional dosing method: tablets. In order to ensure patient compliance and to allow dissolvable films to become a viable delivery system, bitterness masking becomes essential. This paper discusses the research done at Noville to achieve pleasant tasting pharmaceuticals in which bitter actives have been successfully masked. Noville is a flavor and fragrance house dedicated to the research into the masking of various unpleasant tastes together with the development of base formulations and flavors to complement the active ingredients.

THE PHYSIOLOGY & PSYCHOLOGY OF TASTE

To obtain an understanding of the reasoning behind this research, a basic understanding of the physiological and psychological events that occur simultaneously in the experience known as taste is necessary. The earlier teaching of a taste map of the tongue showing distinct areas responding to certain stimuli has been replaced with a new theory. The most recent theory is that all taste buds respond to all stimuli. These stimuli include sweet, sour, bitter, salt, and umami.

Taste buds are onion-shaped structures containing between 50 to 100 taste cells.¹ Chemicals from food or oral ingested medicaments are dissolved by the saliva and enter via the taste pore. There they either interact with surface proteins known as taste receptors or with pore-like proteins called ion channels. These interactions cause electrical changes within the taste cells that trigger them to send chemical signals that translate into neurotransmission to the brain. Salt and sour responses are of the ion channel type of responses, while sweet and bitter are surface protein responses. The electrical responses that send the signal to the brain are a result of a varying concentration of charged atoms or ions within the taste cell. These cells normally have a net negative charge. Tastants alter this state by using varying means to increase the concentration of positive ions within the taste cell. This depolarization causes the taste cells to release neurotransmitters, prompting neurons connected to the taste cells to relay electrical messages to the brain.² In the case of bitter taste, such as quinine, stimuli act by binding to G-protein coupled receptors on the surface of the taste cell. This then prompts the protein subunits of alpha, beta, and gamma to split and activate a nearby enzyme. This enzyme then converts a precursor within the cell into a "second messenger." The second messenger causes the release of calcium ions (Ca^{++}) from the endoplasmic reticulum of the taste cell. The resulting build-up of calcium ions within the cell leads to depolarization and neurotransmitter release. The signal now sent to the brain is interpreted as a bitter taste.³

Based upon the recent theory that taste cells can interpret and process all the different stimuli, a method of diminishing the overall response to one stimulus would be to introduce a second stimulus. This is based upon the assumption that differences among responses to stimuli are not so much a distinction between

firing and non-firing of the neurons, but instead the difference in the amount of firing.⁴ This theory is the basis for the current research being presented in this paper: the ability to transform the responses of certain stimuli by introducing other stimuli. Effective blocking of the taste receptors can be accomplished by either coating the surface pore or competing within the channel themselves to reduce the net effect of the bitter stimuli firings. While the introduction of competing stimuli is part of the masking system, specific flavors and sweetness profiles are essential to complete the experience and produce a pleasant taste for the consumer.

MASKING OF ZINC IN A MOUTHWASH

The initial work in this taste-masking area was prompted by Pfizer with a request to mask the burn of Listerine Tartar Control® mouthwash and block the astringent taste of the zinc chloride. If one would be able to coat the receptors, it would make them non-responsive to the burn of the eucalyptol and alcohol contained in the mouth rinse. A coating material similar to a fat would be necessary. Miglyol was initially tested and, while significantly reducing the burn, it produced a cloudy product that was unacceptable. After screening numerous compounds, a hydrogenated castor oil, Cremophor RH40 from BASF was identified as the perfect coating agent for the receptors because it masked the burn and produced a clear end product.⁵

While the burn of the alcohol and eucalyptol had been significantly reduced, the astringency and metallic taste of the zinc salt had to be dealt with. To accomplish this, a specific flavor was formulated that combined one sweet note, one fruity note, and one spice note. It has been found that the spice note contributes toward reducing the astringency ordinarily imparted by the zinc. The sweet note was discovered 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 helps 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 note may also be selected from among those known in the flavoring art, with raspberry and lemon being preferred. For maximum effectiveness, the flavoring 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. In the current product, preferred amounts are from 0.1% to 0.2% by weight, with 0.15% as the most preferred amount.⁶

Flavor panel evaluations used six trained panelists who evaluated the burn sensation and astringency of three products: experimental masked mouth rinse, Listerine Tartar Control Mouth Rinse, and a commercial non-antiseptic mouth rinse. 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 6-point burning intensity scale in which 6 represents intense burning (as in the taste of the Listerine) and 0 represents no burning (as in the taste of water). Each panelist tasted each product three times with 2 hours between tastings. The 18 evaluations for each data point were averaged and analyzed using the Student T-test at various confidence levels.⁶ Results are presented graphically in Figures 1 and 2.

FIGURE 1

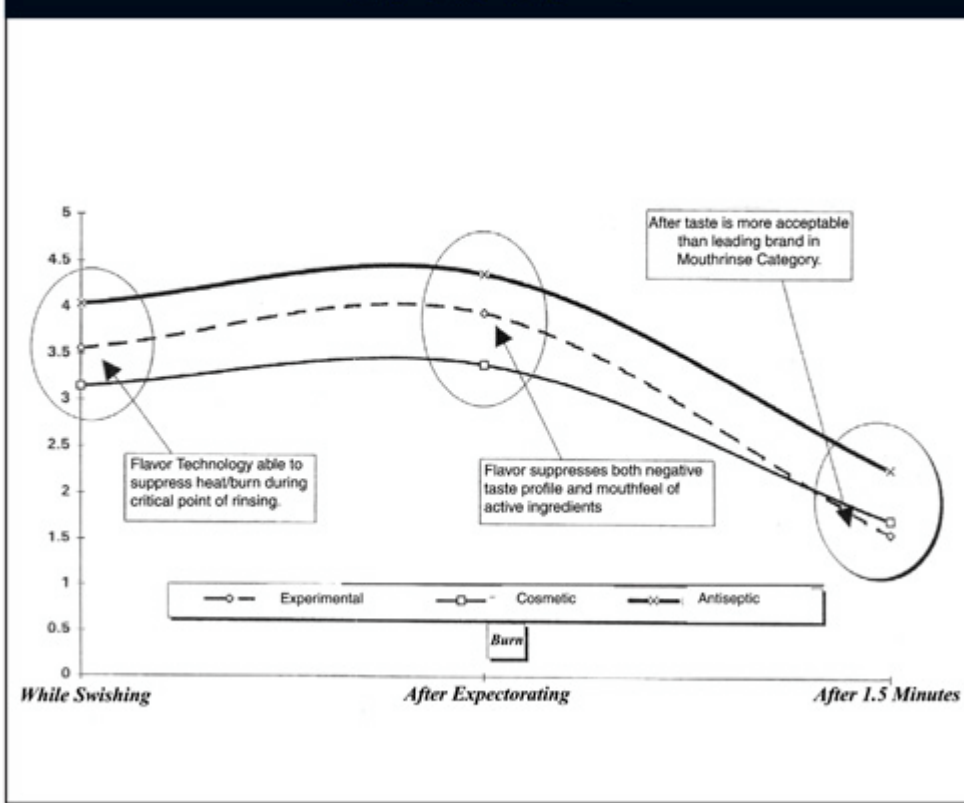


FIGURE 2 (While Swishing)

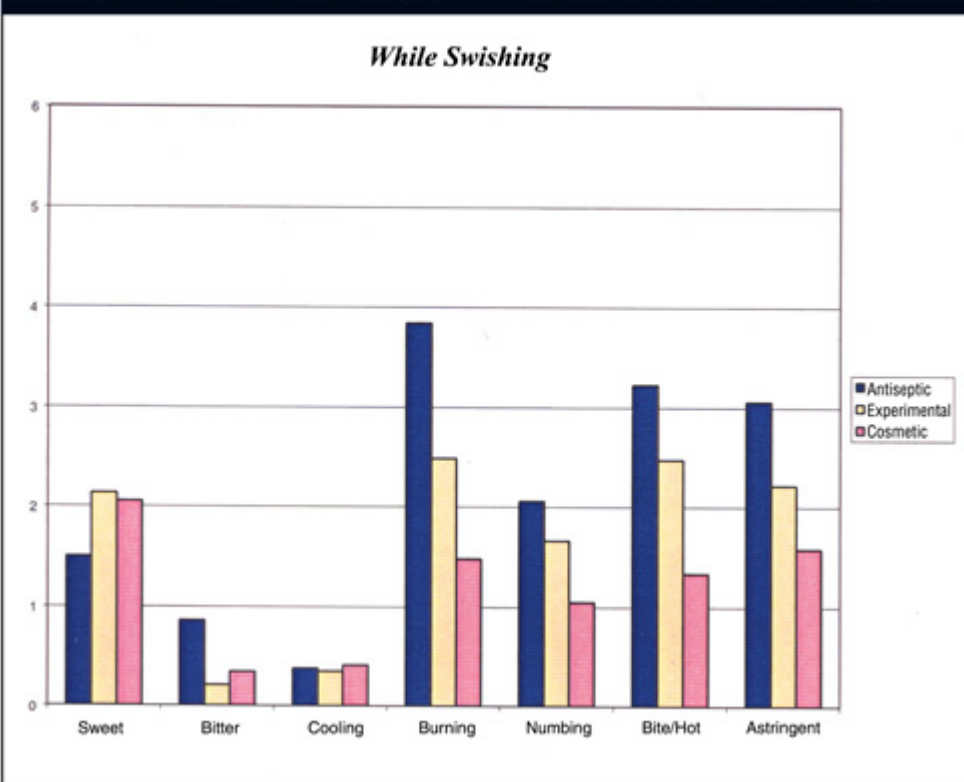


FIGURE 2 (After Expectorating)

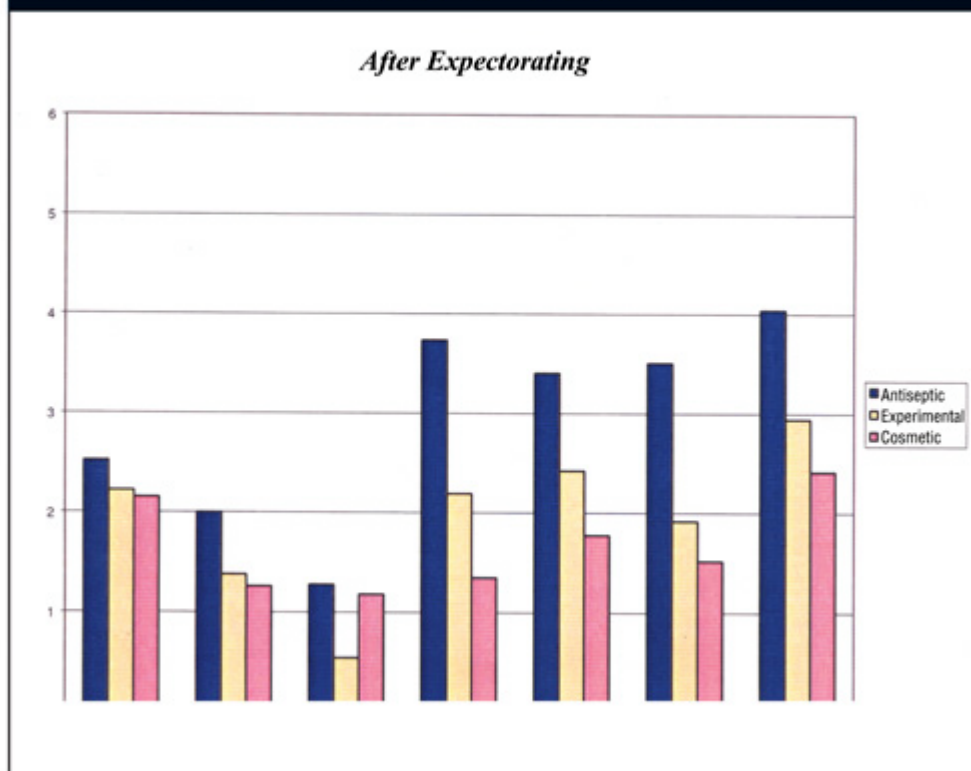
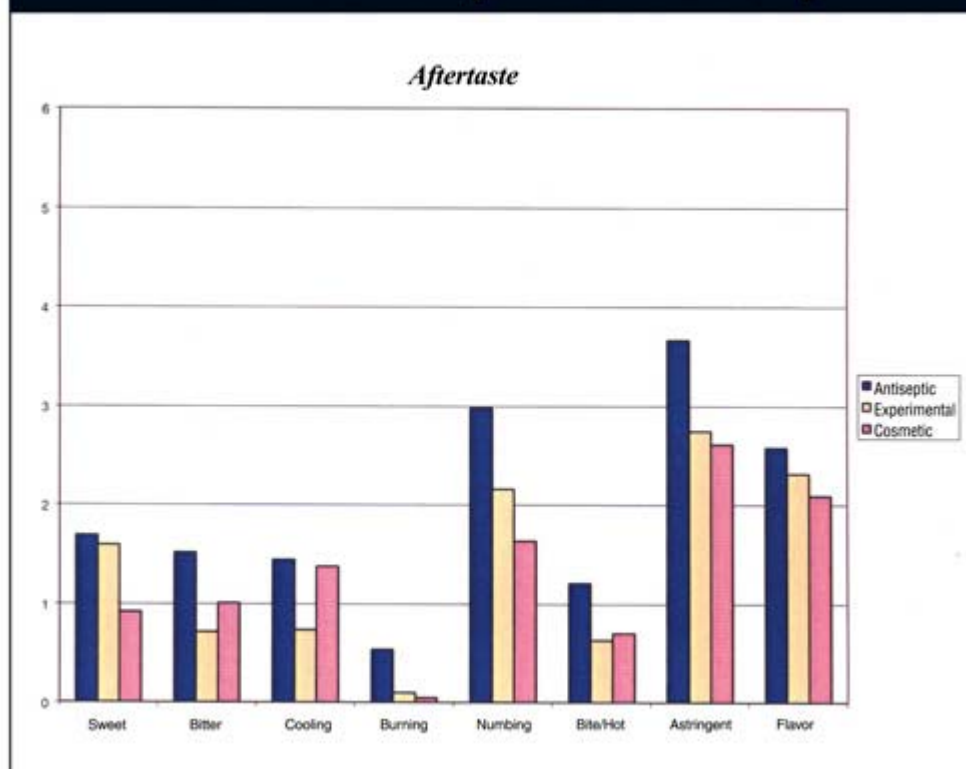


FIGURE 2 (Aftertaste)



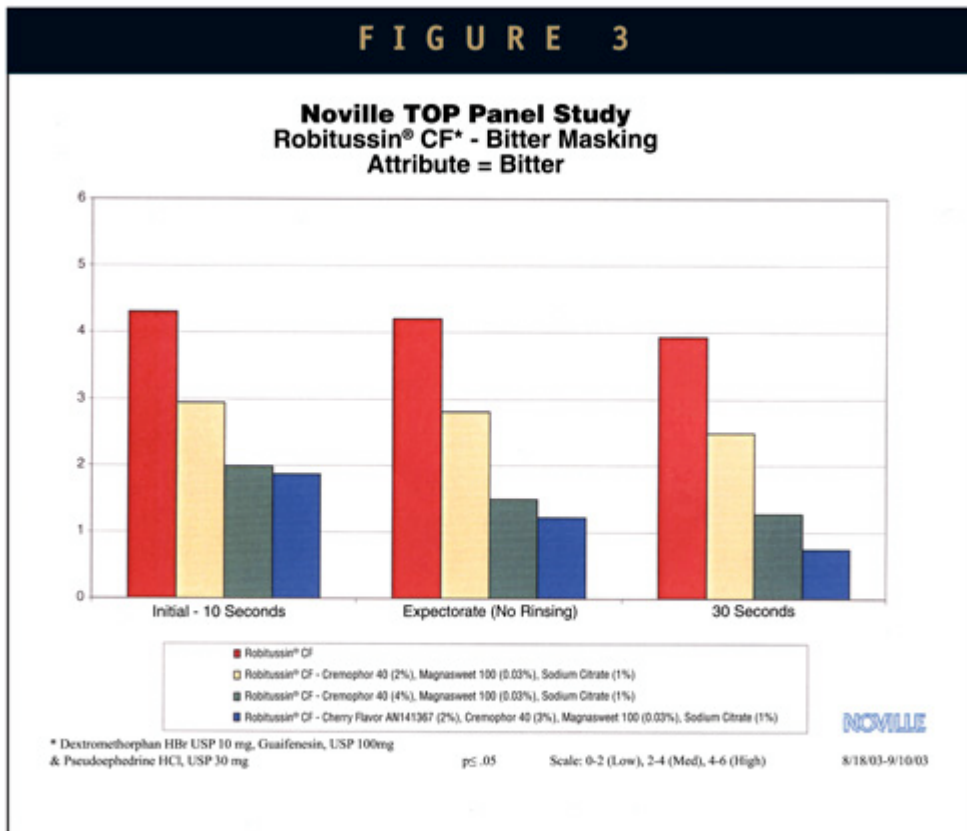
IMPROVING COUGH & COLD PREPARATIONS

Another area of masking bitter actives was in OTC proprietary products, such as cough and cold preparations. Often the bitter taste of these preparations leads to lack of patient compliance, especially with children. These particular systems require not merely blocking or masking agents, but also expertly developed flavors and sweetness profiles that create an entire masking package. It is critical to possess the knowledge of the art when attempting to make such preparations not only palatable but pleasant tasting.

There are a variety of high-intensity sweeteners that can be used either alone or in combination with each other to provide a specific sweetness profile. We have found that using sodium saccharin, which has an initial burst of sweetness but dissipates rapidly, together with MagnaSweet, which has a tendency to build in intensity over time, produces a sweetness profile that extends itself over the time of the product being experienced in the mouth.

MagnaSweet is monoammonium glycyrrhizinate and is available from Mafco of Camden, New Jersey. The specific work done on these products was for Wyeth Labs on their Robitussin cough and cold preparations. The actives that had to be masked were Dextromethorphan HBr, guaifenesin, and pseudophedrin HCl, all of which are bitter and tend to have a lingering unpleasant taste. The bitterness experienced with these actives tends to build in intensity and gravitates to the rear of the oral cavity. A total masking system had to be designed that would not only cover the initial bitter taste but be protracted over the tasting experience. To compete with the bitter receptors neuron firings, sodium citrate, an acid salt, was added causing competition within the receptors.

As the receptors responded to the salt, it reduced the response to the bitter stimuli and caused an overall reduction of the bitter taste. MagnaSweet was used to give an extended sweetness profile. Cremophor was created to coat receptors. A cherry flavor was created to complement the masking and sweetness profiles. The results of this testing by an expert panel is shown graphically in Figure 3. In this case, the successful masking of the bitterness of the actives was achieved in a three-fold approach: physiological competition, sweetness profiling, and flavor creation.

FIGURE 3

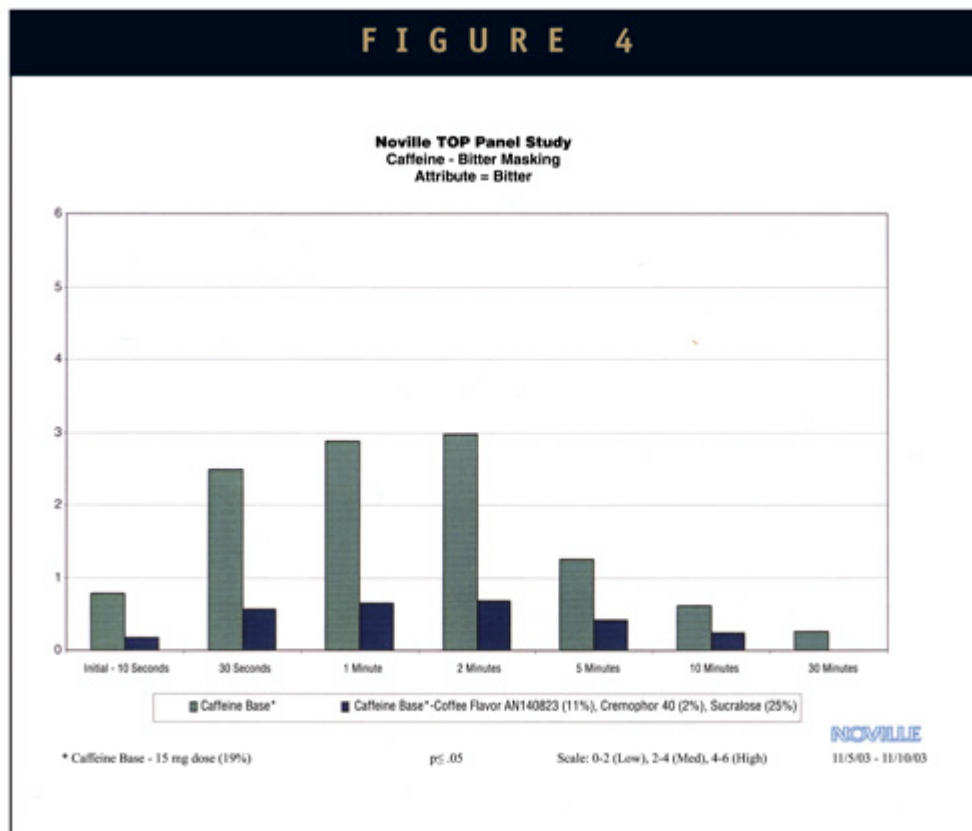
DISSOLVABLE FILMS – A NEW DELIVERY SYSTEM

With the recent introduction of Listerine Breath Strips, a new and very unique delivery system for active ingredients has been developed. These systems employ a water-soluble film-forming polymer in a water-oil emulsion containing active ingredients, flavor, and sweeteners in a film that is extruded and heated to drive off excess water. The finished sheets of film are then cut into strips, which are sized to deliver the correct amount of active ingredients.⁷ This new dosing mechanism has been adapted to the pharmaceutical industry as an alternative method of delivering medication to patients who are unable to use the traditional method of dosing: tablets or pills. By adjusting different levels of the polymers and other ingredients within the matrix of the films, release of the active polymers and other ingredients within the matrix of the films release of the active ingredients can be controlled. With the introduction of this means of delivery, masking of the unpleasant taste of numerous actives has become essential. Almost all pharmaceutical actives are extremely bitter and cannot be tolerated by patients, which is why they are normally formed into coated tablets that are released in the stomach or intestines, eliminating the bitter experience. However, with the advance of dissolvable films, the actives are now experienced within the oral cavity and need to be rendered user friendly.

CAFFEINE – BITTER

We have done a great deal of work with the masking of these pharmaceutical actives with a company engaged in producing dissolvable films, Kosmos Pharma of Kingsport, Tennessee. Kosmos Pharma has developed dissolvable films for the delivery of numerous active ingredients and approached Noville to help with the masking and flavoring of these films. The initial challenge was to mask caffeine, which was being used in a film for a stay-awake type product. We selected the Cremophor RH 40 to coat the taste receptors and added citric acid to compete within the channel receptors with the bitter stimuli. Sucralose was selected as the sweetener. A range of different flavor types was applied to this system, which included mint,

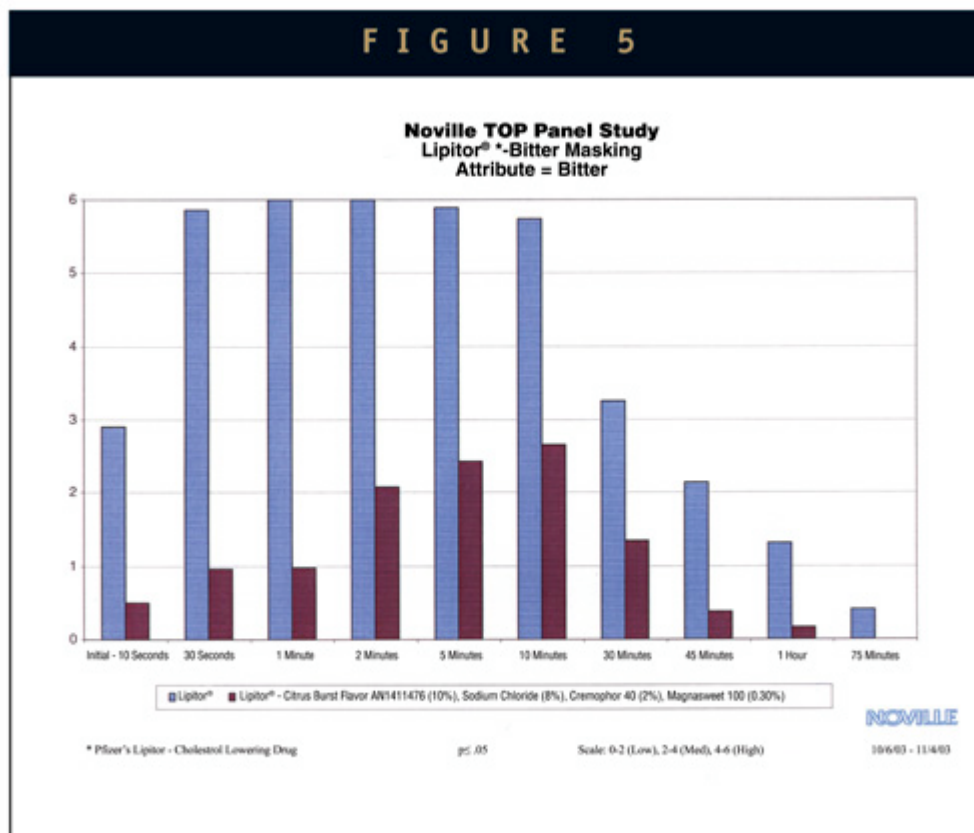
raspberry, lime, citrus, and coffee. When the three-part masking system was added to the finished films, the bitterness of the caffeine was significantly reduced (Figure 4).



LIPITOR – BEYOND BITTER

We next were challenged with masking the extremely bitter active Calcium Atovastatin, the active in Pfizer’s Lipitor. A great deal of work has been done using sodium chloride to reduce the overall perception of bitterness.⁸ We selected sodium chloride to compete within the channel receptors with the bitter stimuli to reduce the overall perception of bitterness. **An extended sweetness profile was developed using Sucralose for initial sweetness burst and MagnaSweet for extended sweetness.** A citrus mint flavor with menthol was chosen because the cooling effects of the menthol served to distract the organoleptic effects of the bitter taste. Cremophor was added to coat the receptors. By combining the physiology of the taste receptor actions with the art of complimentary flavor creation, this extremely bitter active was successfully masked (Figure 5).

FIGURE 5



BITTERNESS ELIMINATED

In conclusion, it has been demonstrated that the new current theory as to taste responses in the oral cavity is in fact valid. By using this theory and employing competitive sensory stimuli, reduction in the overall perception of the negative stimuli was achieved within the channel receptors. Surface protein receptors were masked via a coating action of the Cremophor. In order to create a palatable drug delivery system, other factors must be combined with the masking system. These include a sweetness profile, which is designed for the specific actives and/or system being used to deliver the actives, together with a flavor that is formulated specifically for the system involved. It is the combination of the masking technology, the appropriate sweetness profile, and a specific flavor that results in a successful elimination of bitterness. This system is cost effective when compared to encapsulation or highly structured molecular systems. By using the latest physiological theory with respect to taste and combining that with the art of flavor creation, a sensory change is achieved within the oral cavity, and bitterness normally associated with these actives is completely eliminated.

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BIOGRAPHY



Dr. Roger E. Stier is Technical Director of the Flavor Division of Noville, Inc., in South Hackensack, New Jersey. He has spent 30 years in oral hygiene research being responsible for the reformulation of Aquafresh toothpaste. He holds 10 U.S. patents and 3 patents now under review. His area of expertise is masking systems and base creation for oral hygiene and pharmaceutical products. Dr. Stier earned his BS from Fairleigh Dickinson University and has been elected to Who's Who in Science & Engineering. He earned his PhD in Chemistry from Stafford University, London, Ontario, Canada.