A STUDY OF FLAVORING ANS MASKING AGENTS

by

DELBERT GEORGE SCHNEIDER

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The sense of taste is of great importance in the administration of medicaments. The taste of a medicinal preparation will in many cases affect the efficacy of the drug. A patient is better satisfied with the use of a preparation which is pleasant to take. It is for this reason a doctor attempts to make the consumption of medicinals as pleasant as possible by prescribing the drugs in preparations which are palatable. It is to the advantage of the pharmacist to know the many manners of making most prescriptions palatable. The pharmacist should know the basic ideas and fundamentals behind taste, the manners of affecting taste and methods of flavoring and taste masking to aid the doctor in his goal. This field could well be an excellent means of bettering the relationship of the pharmacist and the physician. This is a compilation of available material by various authors and the results of personal experimentation.

Taste is defined as "a sensation excited by stimulating the sense of taste, popularly, the blend of sensations obtained from a substance in the mouth, and consisting of taste sensations proper, plus tactile and olfactory sensations excited by the substance"[1]. Only four tastes are fundamental: salt, sour, sweet and bitter. All other tastes are a combination of these basic four or are sensations of taste modified by smell, temperature and touch.

1. Webster's New International Dictionary, Second Edition, Unabridged, 1934

The sensation of taste is a direct result of the stimulation of the various and many taste buds in the mouth. The adult person has these taste buds occuring on the tongue, the soft palate, epiglottis, and the beginning of the gullet. A child is better fitted for taste reception. A younger person has taste buds over the whole surface of the tongue, and on the insides of the cheeks as well as the areas found in the adult mouth. This accounts for the tendency of children to prefer sweets, whereas adults prefer flavors in which the odoriferous parts play an important role.

The sense of smell is much more acute in man than the sense of taste. Evidence of this fact may be gotten by comparing the minimum stimuli for these two senses. The minimum stimulus is that quantity of matter which wakes the first sensation of the sense. The figures given are for ethyl alcohol, C_2H_5OH, it being one of the few substances which have odor and taste independent of each other. Moncrief[2] gives the following figures for the lowest concentrations of ethyl alcohol that can be smelled and tasted: Smell: 0.44% wt./wt. in air

Taste: 14.0% wt./wt. in water

It is readily seen by comparing the above figures that smell is about thirty-two times as delicate as taste, in the case of ethyl alcohol. In interpreting these figures, it is obvious that it is possible to make a preparation which should, but will not, have a pleasant taste, due to some osmophoric substance unpleasing to the person. Thus a substance with an unpleasant smell or odor will usually have an unpleasing taste although a bad tasting sub-

2. Moncrief, R. W. The Chemical Senses, 1st ed.

stance may have no odor at all or an odor that is not unpleasant. If a preparation or a substance has a bad taste and a bad odor, efforts to cover the taste and give to the preparation a pleasant taste will usually be of no avail, unless you give to it a likewise pleasant odor or remove the odor entirely and then give it a pleasing taste. Thus it is easy to give a pleasing taste to an odorless, tasteless preparation, a little more difficult to produce a pleasing taste when some material has a bad taste and no odor, and extremely difficult when some ingredient has a bad taste and a bad odor. Flavoring and masking the taste will therefore involve masking the odor as well. Many of the agents to be discussed in this work are effective in masking the odor.

As stated before, the multitude of tastes are due not only to taste sensations, but also to temperature and smell. Just as one odor may mask another, so may one taste dusguise another. Syrups of cinnamon, orange and sarsaparilla disguise a salty taste and the syrups of raspberry and cocoa will disguise a bitter taste. To be able to mask the taste of almost any substance the person undertaking the task should be able to tell what effect the chemical structure of the compound, the temperature and the odor will be on the taste of the substance. The person should be able to tell this by observing the conditions mentioned. By studying the basic tastes, the chemical structure of some compounds which have one of the four basic tastes, the effect of temperature variations, and odor, we can obtain some of the knowledge required before studying the methods of masking tastes and flavoring preparations and the agents used for these purposes.

The four basic tastes are salt, sour, sweet and bitter. These tastes may occur in compounds singly or together. For example, the salt taste is usually associated with some other taste, such as we say a substance has a salty bitter taste or a salty then bitter taste. It is also known that a substance may have more than one taste. A substance may taste sweet at the tongue tip and bitter at the back of the mouth. Bittersweet is an example of this type compound. A compound may taste salty at the tip of the tongue and bitter at the back of the tongue as in the case of epsom salts. Then again, a substance may have an initial taste and an after taste. Saccharin, for example, has a primary sweet taste followed by a bitter after taste.

The sour taste is associated with acids. It depends on the presence of the hydrogen ions formed upon ionization of the acid in water or in the saliva. The taste depends on these ions but is modified by the presence of undissociated molecules of the acid. Since it is characteristic of an acid to ionize into hydrogen ions and an ion, anion, such as the chloride or sulfate ions, the stronger the acidic characteristics and the sour taste. The sour taste is generally proportionate to the hydrogen ion concentration. Temperature affects the sour taste in that a warm acid solution is more sour than a cold solution of the same concentration of the same acid.

The sensation of saltiness is due to the anion and the cation. If this were not true, all salts of the sodium series would taste the same and all sulfates likewise would taste the same. We know this is not the case if we recall the tastes of common table salt, sodium chloride, and baking soda, sodium bicarbonate. The salt taste is increased by a lowering of temperature. A cold

salt solution is more salty tasting than a solution of the same concentration of the same salt at higher temperature. The requirement for a salt taste is the compound must be an ionized salt of low molecular weight.

The bitter taste is much more sensitive than the other three. A very small amount of a bitter substance is readily detected by taste. Alkaloids such as quinine are readily detected by their bitter taste in very minute quantities. Quinine hydrochloride can be detected in a 0.0016% solution. The bitter taste is found in a great variety of substances, but is closely associated with several classes of compounds. These classes include the alkaloids and nitrocompounds, such as picric acid, and the salts of magnesium and the heavy metals. The nitro compounds are bitter especially if there are two or more nitro groups in the compound, and in the case of the metallic salts the metallic ion is the determinant factor in the sensation of bitterness.

The sweet taste is produced by a variety of compounds, especially if they are of organic nature and non-ionizing. The presence of many hydroxyl groups is usually evident of a sweet taste, and it also depends in the case of the metallic salts on the metallic ion. It is seen that increasing concentrations will give increased sweetness and an increase in the temperature of a solution of known concentration will increase it.

It was previously stated that the sense of smell played an important role in the sense of taste. The flavor of a substance such as a food stuff depends largely on the temperature at which it is consumed because of the role of the sense of smell. Olfaction is known to be influenced by temperature and the substance becomes more odoriferous upon warming. Thus it is that

meat or coffee have more flavor when warm. An increase in the temperature increases the sensations of sweet and sour, but decreases those of salt and bitter. The sweet and sour substances are usually of a more volatile nature and thus with an increase in temperature more of the odor of the substance is perceptible and the taste is affected accordingly.

Study of the factors affecting structure and their relationship to taste must be extended to determine what effects are evidenced by the introduction of certain groups or radicals. Thus we will study the effect of the introduction into the molecule of the more important groups.

The entry of an alkyl group is often followed by slight alterations of the taste, as in the case of homologous compounds, and anything regarding taste may happen. Alkylation of amides or amines where the group is attached to a nitrogen atom frequently produces a sweet taste. Attachment to an oxygen atom causes reduction in the potency of the taste possessed by the compound before the alkylation took place.

The phenyl group has an effect of causing bitterness or tastelessness, regardless of where it is substituted in the molecule. The tastelessness in water solutions is usually due to the insolubility of the formed aromatic compound in water.

The hydroxyl group is in most cases associated with substances having a sweet taste. Sweetness then may be predicted for a compound possessing one or more hydroxyl groups. Sweetness is usually associated with this structure : R-CH(OH)-C:CH-, where R is a normal aliphatic chain.

Moncrief states that the general case is that the introduction of an R-O- group will produce a sweeter compound. The

presence of the alkoxy group can usually be thought indicative of sweetness.

The esters of inorganic acids are sweet, and most esters of organic acids are bitter.

The presence of a nitro group usually indicates bitterness which is increased with the increase in the number of the nitro groups. The introduction of an amino or amido group into a compound is associated with sweetness.

Nitrogen containing basic compounds are bitter, acid compounds containing nitrogen are sour or bitter, and neutral compounds are most often sweet.

Bitterness is usually produced by the introduction of a halogen atom into the molecule. This is due to the halide itself and to the increase in the molecular weight. Substitution in an aliphatic hydrocarbon indicates sweetness and bitterness in the aromatic compounds. Iodine has the greates bittering effect because of its great molecular weight and flourine with the lowest weight of the halide series has the least effect.

Sulfur is usually associated with a foul odor. Because many compounds containing sulfur do have disagreeable odors, the taste of these compounds can not be expected to be pleasant. This type compound is another example of the effect of the sense of smell on the sense of taste.

Moncrief found that there is no definite rule which can be drawn regarding the effect of isomerism, except that isomers usually do not have the same taste or if they do possess the same taste they do not possess them to the same degree.

The National Formulary and the Pharmacopoeia of The United States, realizing the value of making disagreeable preparations

palatable contain many flavoring and masking agents. The pharmacist must know these agents and their use in the extemporaneous filling of prescriptions as well as the unofficial manners. We will study these various agents and the usage of them in masking and flavoring techniques. Among the agents found in the official volumes are:

Oil Sugars: Volatile oils with sugars, wherein the oil imparts a pleasant odor and the sugar gives a better taste to the preparation.

Elixirs: The oils in sweetened hydroalcoholic medium; the oil for bettering the odor and the sweet medium for bettering the taste.

Syrups: The oils in a sweetened water medium in which case the oils are again for bettering the odor and the sugar for the flavor. This class also contains fruit flavors in the sweetened medium.

Crude Drug: The crude drugs or extracts of the crude drug, such as ginger or balsam of tolu, are used for flavoring preparations.

Sweetening agents: This group includes such things as the sugars, saccharin, glycerin, and coumarin which are used for flavoring and masking the taste of various preparations.

Among the manners available to the pharmacist for masking disagreeable tastes are: Effervescent powders or tablets, emulsification, overshadowing one taste with a stronger, more palatable taste, and colloidality.

The masking of tastes by use of effervescent powders or tablets is of value when the prescription is for dry powders which when taken will have a disagreeable taste. Their use is based on the tartness of carbonic acid which is liberated at the time the medicine is taken. The carbonic acid is liberated due to an interreaction between the bicarbonate present and the added tartaric or citric acid. The carbonic acid masks the taste of the disagreeable substances due to its tartness. The National Formulary VII contained ten preparations in which use was made of the effervescent powders. Common everyday use is made of this theory in such commercial preparations as Bromo Seltzer and Alka Seltzer.

Emulsification is another easy manner of masking a taste undesirable in a preparation which is liquid in nature. The pharmacist knows the technique of emulsification, and the general rule he must remember is: If the substance is soluble in oil, disperse the substance in the oil and disperse the oil in water with subsequent flavoring of the water. If the substance with disagreeable taste is soluble in water and insoluble in oil, dissolve the substance in water, disperse the water solution in oil and flavor the oil phase.

Overshadowing the disagreeable taste with a stronger palatable taste is an easy manner for use in general prescription work. Much work has been done in this phase of taste masking. Former work done by various workers have led to the following agents' acceptance in the masking of compounds having one of the four basic tastes.

Inorganic Halide Salts: These substances which have salty tastes by Fantus[3] by the use of glycyrrhiza, which is also used

3. Journal of the A. Ph. A. vol. 23, 1934

in commercial preparations. Purdum[4] also advocated the use of glycyrrhiza. Wright[5] stated that people did not like the taste of glycyrrhiza and recommended the use of gycerin which he thought improved the flavor as well as masking the taste.

Acids: All of the above mentioned men agreed that the sour taste of the acids was best masked by fresh fruits and their preparations, such as syrup of cherry. There would be the possibility of incompatibility in the prescriptions containing acids if any basic vehicles were used, but this possibility is eliminated by the acidity of the fruit preparations.

Salicylates and Iron Salts: Cinnamon in the form of syrup of cinnamon was recommended by all the three men as the masking agent of choice for this type compound.

Bitter Substances: The bitter substances, such as the alkaloids, are the most difficult to mask, with only half of the usual dosage masked with overshadowing agents. The technique in this case is to keep the dosage low and take the preparation more often. Fantus recommends the use of aromatic syrup of eriodictyon because it will mask the taste and does not give much bitter after taste.

Sharp Tasting Substances: Urea is a good example of a sharp tasting substance which is difficult to mask and Fantus used the colloidal vehicles such as syrups of acacia and eriodictyon.

4. Year Book of the A. Ph. A., 1921, vol. 10

5. Remington's Practice of Pharmacy, second edition, 1926

Sweet Compounds: There is very little necessity of masking a sweet taste, since very few people are sensitive to a sweet taste. Therefore no work was done on this phase of masking.

The overshadowing power of many of the more common flavoring agents was tested in an attempt to find the best agent for the various type compounds. Solutions of the drugs included in the tests were made with the designated amount of each drug contained in each five cc of final solution. Five cc of the vehicles were placed in test-tubes and solutions of the drugs tested were added drop by drop to the vehicle. After each addition, the preparation was shaken vigorously and the preparation tasted and the process continued until the taste of the drug was just perceptible.

A solution of each of the following drugs, in the concentration listed, was made. Sodium bromide, 5 grains/5 cc

Sodium salicylate, 2½ grains/5 cc

Codeine sulfate, ¼ grain/ 5 cc

Urea, 15 grains/5cc

Chloral hydrate, 5 grains/5 cc

Five cubic centimeters of the following vehicles masked:

Sodium bromide

Vehicle:	Amount masked:
Syrup of cherry	2 grains
Syrup of glycyrrhiza	2 grains
Aromatic elixir	1 grain
Elixir lactated pepsin	2 grain
Glycerin	1 grain
Peppermint water	2 grains

Sodium Salicylate

Vehicle:	Amount masked:
Syrup of cherry	5 grains
Syrup of Cinnamon	5 grains
Cinnamon water	5 grains
Syrup of tolu	5 grains

Codeine Sulfate was masked only by Syrup of cherry.

Urea

Vehicle:	Amount masked:
Syrup of acacia	3 grains
Syrup of cinnamon	3 grains
Syrup of raspberry	4 grains
Syrup of eriodictyon	1 grain
Syrup of Glycyrrhiza	5 grains
Aromatic elixir	4 grains

Chloral hydrate

Vehicle:	Amount masked:
Syrup of wild cherry	0 grains
Syrup of raspberry	1 grain
Syrup of tolu	1 grain
Syrup of glycyrrhiza	1 grain
Syrup of chocolate	2 grains
Syrup of orange	2 grains

In summarizing the results of the experimentation with overshadowing agents, it was found that the best agents for the masking of the basic tastes were:

Salt: Syrups of Cherry, Glycyrrhiza and Peppermint

Sour: Syrups of tolu, eriodictyon and cherry

Bitter: Syrups of eriodictyon, tolu and cherry

Colloidality is a more recent and less studied manner of masking taste. The colloidal suspensions or gels exert their masking effect by the phenomenon of adsorption. This is the phenomenon of the collection of a gas or vapor, or solid on the surface of a solid. The adsorbent is usually a porous solid with an immense total surface area. The immense surface area is desirable since the adsorbing power of the adsorbent is proportionate to the surface area. The phenomenon takes place as the result of a weak interaction between the solid and the adsorbed substance, as in condensation, or as the result of a strong inter-attraction between the substances, as in the case of a chemical reaction.

It may also be the result of an electrical attraction. A colloidal suspension possessing a negative charge will attract particles which are characterized by a positive charge, and vice versa.

Some of the first work done in the study of vehicles which mask the tastes by adsorption was done by Fantus and his coworkers. Fantus found that "Eriodictyon preparations are, at the present, chiefly used as disguising vehicles for bitter remedies, such as quinine; for which purpose they were first recommended by Rother[6] who believed that this disguising value depended upon the formation of insoluble quinine resin salts from which the quinine could be readily assimilated.

"Eriodictyon lessens the bitter taste by adsorption, but does not, however, lessen the taste sensations of sour, salty, sweet or acidity. This adsorption can be shown to be based on electrical charges; the resinoid, the active principle of Eriodictyon, is electronegative. When a dye such as methylene blue, a basic dye, is added to a solution of the resinoid, the basic dye is adsorbed or attracted by the resinoid. However, an acidic dye, such as eosin, is not removed in any great amount from solution.

"Eriodictyon can only be used in slightly basic solutions, being incompatible with acids and acid salts. It is also incompatible with alkali, because an alkaline excess dissociates the alkaloid-resin compound. It can not be used with iron salts, or oxidizing or reducing agents."

6. Rother, American Journal of Pharmacy, vol. 59, 1887

In summarizing Fantus' and his coworkers' work find: 1) The active principle of eriodictyon as far as the disguising power is concerned is the resin; 2) The resin acts by a process of adsorption, which is specific for bases only, as is evidenced by positive results with alkaloids and alkaline dyes, and negative results with acids and acidic bitter substances such as phenobarbital; 3) Only the bitter taste of basic bodies, when given in very small doses or of slight bitterness, can be satisfactorily disguised by eriodictyon.

Fantus stated that the effect of masking tastes by the use of colloidal substances such as eriodictyon was the result of electrical attraction. With that in mind, the power of three of the most common substances which form colloidal gels with water was determined. Solutions were made of the substances in the most common percentages used, and five cubic centimeters of the solution were placed in a test-tube. Solutions of the medicinals to be masked were added drop by drop to the vehicle in the test-tube. After each addition and subsequent shaking, the solutions were tasted. The results are listed in the following tables.

Five cc. of a 2% solution of Pharmagel A, which forms a positive colloid, masked the taste of:

1.25 cc of a 20% solution of urea or .25 Gm. of urea.
7.5 cc of a 15% solution of sodium salicylate or 1.1 Gm.
2.5 cc of a 5% solution of ascorbic acid or 0.1 Gm.
6.3 cc of a 25% solution of sodium bromide or 1.5Gm.
1.56 cc of quinine hydrochloride or 0.008 Gm.
4.00 cc of a 10% solution of sodium phenobarbital or 0.4 Gm.

It can be seen that this positive colloid masked more of a substance which owes its taste to the negative ion than of a substance which owes the taste to the positive ion.

Five cubic centimeters of the official Mucilage of Acacia, which has a negative charge, masked the taste of:

2.3 cc of a 10% solution of sodium phenobarbital or 0.23 Gm.
6.0 cc of a .5% solution of quinine hydrochloride or 0.03 Gm.
4.0 cc of a 25% solution of sodium bromide or 1.0Gm.
9.0 cc of a 5% solution of ascorbic acid or 0.45 Gm.
3.2 cc of a 20% solution of urea or 0.64 Gm.
5.0 cc of a 15% solution of sodium salicylate or 0.75 Gm.

Five cubic centimeters of a 2% solution of methylcellulose, which forms a neutral colloid, masked the taste of:

3.2 cc of a 10% solution of sodium phenobarbital or 0.26 Gm.
1.2 cc of a .5% solution of quinine hydrochloride or .006 Gm.
2.5 cc of a 25% solution of sodium bromide or 0.63 Gm.
1.5 cc of a 5% solution of ascorbic acid or 0.08 Gm.
1.3 cc of a 20% solution of urea or 0.26 Gm.
5.3 cc of a 15% solution of sodium salicylate or 0.8 Gm.

Conclusions: For masking the taste of compounds, such as sodium phenobarbital, which owe their taste to the negative ion, it was found that the positively charged colloids were best. For those compounds, the taste of which is due to the positive ion, such as quinine hydrochloride, the negative colloids were best. Neutral colloids were efficient in most cases where no electrical attraction was shown, as in the case of sodium bromide where the taste is due to both ions. Electrical repulsion, as in cases of attempts to mask positive ions with positive colloids, greatly decreased the adsorbing power.

In the use of overshadowing agents, syrups of cherry, glycyrrhiza, and peppermint were found best suited for masking salty tastes, syrups of tolu, eriodictyon and cherry for sour and bitter. It was found that a slight pleasant taste retained its palatability for a longer period of time than a stronger taste.

An excess of any masking agent or flavoring agent should not be used. The rule is: use only the amount of the masking agent

necessary to cover the unpleasant taste and then add in excess only that amount of the flavoring agent needed to give the preparation a slight palatable flavor. Children prefer the flavors of anise, fennel, coriander, licorice, and sarsaparilla. Adults prefer the fruit flavors: orange, pineapple, cherry, and lemon.

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Assoc. Prof. of Pharmacy

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