



Taste Masking: A Pathfinder for Bitter Drugs

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ABSTRACT

Most of the pharmaceuticals are administered by the popular route of drug delivery, the oral route. Taste is an important and critical parameter in administering formulations which come in contact with the taste buds. Many drugs have bitter taste, thus this is one of the important formulation problem encountered. Due to the bitter taste of the drug there is a constant problem in the treatment of the patients due to their inability or unwillingness to swallow such formulation specially, in children and elderly. Thus, masking of unpleasant taste characteristics of drug is an important factor in formulation of these agents. This lead to the development of taste masking technologies which improved the characteristics of the dosage form and good patient compliance is achieved. The present review depicts the various approaches like use of flavorants and sweeteners, coatings, microencapsulation, prodrug, use of lipoproteins, ion exchange resins, inclusion complex formation, salt formation, granulation and by multiple emulsions. It also includes the commercially used technologies and the methods for evaluation of the taste masking effect.

Keywords: Taste, bitter, commercial technologies, evaluation of taste masking

INTRODUCTION

The word flavor refers to a mixed sensation of taste, touch, smell, sight and sound, all of which combine to produce an infinite number of gradations in the perception of a substance. The four primary tastes – sweet, bitter, sour and saline; appear to result from physicochemical and partly from psychological action. Taste buds, located mainly on the tongue, contain very sensitive nerve endings that react, in the presence of moisture, with the flavors in the mouth, and as a result of physicochemical activity, electrical impulses are produced and transmitted via the seventh, ninth and tenth cranial nerves to the areas of the brain that are devoted to the perception of taste. The brain, however, usually perceives taste as a composite sensation, and accordingly, the components of any flavor, are not readily discernible. Children have more taste buds than adults and hence are more sensitive to tastes.

Taste partly depends on the ions that are produced in the mouth, but color and sound also play a definite role when certain reflexes become conditioned through custom and association of sense perceptions. Also color and taste must coincide e.g., cherry flavor is associated with red color.

Other physiological and physical factors that also may affect taste are coarseness or grittiness due to small particles; e.g., ion exchange resins. Antidiarrhoeal preparations have a chalky taste. Menthol imparts a cool taste because it affects the coldness receptors. Mannitol gives a cooling sensation when it dissolves because, its negative heat of solution causes the temperature to drop. For this reason, mannitol often is used as the base for chewable tablets.

Taste and its physiology^{2,3}

Physiologically, taste is a sensory response resulting from a chemical stimulation of taste buds on the tongue (Figure 1). The sense of taste is conducted to the brain by a process called taste transduction. This process begins with the interaction of tastant (i.e., food or medicine) with taste receptor cells in the taste buds. The tastant binds with G-protein coupled receptors in the cells, triggering the release of a G-protein called gustducin. Taste sensation begins when gustducin activates the effector enzymes phosphodiesterase 1A or phospholipase C-2. The effector enzymes then change the intracellular levels of secondary messengers such as cyclic adenosine monophosphate (cAMP), inositol 1, 4, 5-triphosphate (IP3), and diacylglycerol (DAG). The secondary messengers activate ion channels, including calcium channels inside the cell, and sodium, potassium and calcium channels on the extracellular membrane. This ionization depolarizes the cell, causing the release of neurotransmitters that send a nerve impulse to the brain that carries the signal of taste.

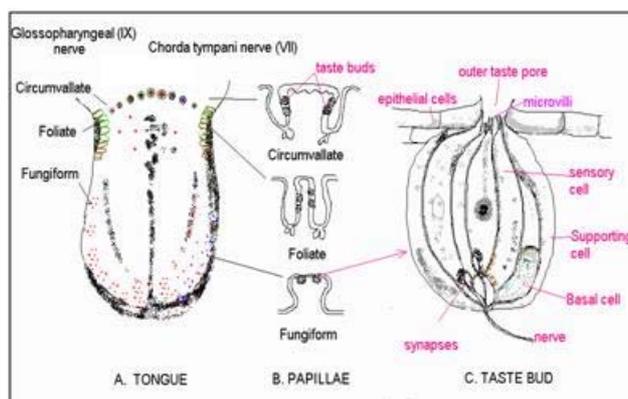


Figure 1: Tongue



Types of tastes¹

The sense of taste is equivalent to excitation of taste receptors, and receptors for a large number of specific chemicals have been identified that contribute to the reception of taste. These include receptors for such chemicals as sodium, potassium, chloride, glutamate and adenosine.

Despite this complexity, five types of tastes are commonly recognized:

- Salty
- Sour
- Sweet
- Bitter
- Umami

Correlation of chemical structure with flavor¹

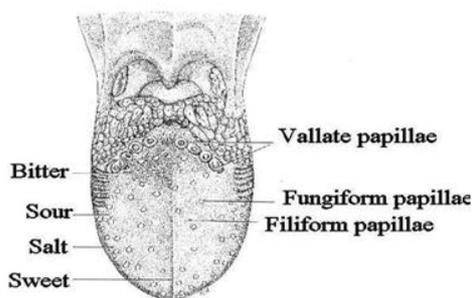


Figure 2

The compounds employed as flavors in vehicles vary considerably in their chemical structure, ranging from simple esters (methyl salicylate), alcohols (glycerin) and aldehydes (vanillin) to carbohydrates (honey) and the complex volatile oils (anise oils).

There is a close relationship between chemical structure and taste. Solubility, the degree of ionization, and the type of ions produced in the saliva definitely influence the sensation interpreted by the brain.

Sour taste is caused by hydrogen ions, and it is proportional to the hydrogen ion concentration and the lipid solubility of the compound. Saltiness is due to simultaneous presence of anions and cations; eg, potassium bromide, ammonium chloride and sodium salicylate. It is characteristic of acids, tannins, alum, phenols, and lactones. High molecular weight salts may have a bitter taste.

Sweet taste is due to polyhydroxy compounds, polyhalogenated aliphatic compounds and amino acids. Amino and amide groups, especially if the positive effect is balanced by the proximity of a negative group, may produce a sweet taste. Sweetness increases with the number of hydroxyl groups, possibly, because of increased solubility.

Free bases such as alkaloids and amides give bitter taste. Polyhydroxy compounds with a molecular weight greater than 300, halogenated substances, and aliphatic thio compounds also may have bitter taste on compounds.

Table 1: Examples with chemical structure of compounds of pharmaceutical interest, representing each of the four primary tastes⁴

Primary Taste	Functional group(s)	Natural Source	Pharmaceutical Examples	Chemical Structure
Bitter	Organic Amines	Poisons, Alkaloids	Quinine	
			Lopiramide	
Sour	Organic or inorganic acid	Natural products, Spoiled food	Ascorbic acid	
			Malic acid	
Sweet	Sugars and sugar analogs	Nutritional and synthetic sweeteners	Fructose	
			Saccharin	
Salty	Inorganic salts	Sea water, mineral deposits	Sodium chloride	NaCl
			Potassium iodide	KI

Factors that are taken into consideration during the taste masking formulation include:⁵⁻¹⁰

- Extent of the bitter taste of the API.
- Required dose load
- Drug particulate shape and size distribution
- Drug solubility and ionic characteristics
- Required disintegration and dissolution rate of the finished product
- Desired bioavailability
- Desired release profile
- Required dosage form

APPROACHES OF TASTEMASKING

- Use of flavorants and sweeteners
- Application of coatings
- Microencapsulation
- Use of lipoproteins
- Prodrug formation
- Inclusion complex formation
- Use of Ion exchange resins
- Formation of multiple emulsions
- Salt formation

- Granulation

USE OF FLAVORANTS AND SWEETNERS

Taste enhancing additives includes the use of sweeteners and other flavorants that can disguise or mask the taste of an unpleasant active. Using a combination of sweeteners and flavors to overpower an unpleasant taste is, unfortunately, the most common approach to taste masking. This simplistic approach is problematic for a number of reasons. Sweet excipients do not provide a best stimulus for the receptors that are tuned for bitterness, and by themselves they are not completely effective at eliminating the taste of extremely bitter (especially extremely water-soluble) actives. They can, however, be more effective in covering up a sour taste. Taste enhancing additives such as sweeteners can be highly effective when used in combination with another primary taste masking strategy.^{4,11,12}

Sweeteners are typically very soluble and are removed from the taste receptors rapidly. A possible way to compete at an appropriate time scale could be to add extended release granules which could continue to deliver sweetness to the taste receptors over the duration of bitterness (10 to 60 seconds) with granules or a solubility retardant.

Flavoring and perfuming agents can be obtained from either natural or synthetic sources. Natural products include fruit juices, aromatic oils such as peppermint and lemon oils, herbs, spices and distilled fractions of these.¹³

Table 2: Flavouring and Sweetening^{14, 18}

Author	Drug	Flavourant / Sweetner	Result
Havli et. al	Cetirizine dihydrochloride	Grape, vanilla	Taste masking of the drug achieved.
Mishra R. et. al	Cetirizine hydrochloride	Aspartame, sucralose, lemon flavour and citric acid	Optimized taste masked rapid dissolving films was obtained with Aspartame, Sucralose, lemon flavor and citric acid.
Ousama et. al	Epinephrine	Aspartame, Acesulfame potassium	Combination of ASP and ASK is more effective in reducing bitterness of drug.
Francesco C et.al	Nicotine Hydrogen Tartrate	Milk-mint	Combination of milk – mint masks bitter taste of nicotine, but this formulation is perceived as irritant in mouth (fast dissolving films).
Russell et. al	Denatonium benzoate	Sodium cyclamate, Zinc sulfate	Mixture of Zinc sulfate and Na cyclamate effective for bitterness inhibition (Zn) and masking (cyclamate).

APPLICATION OF COATINGS

The classic application for taste masking was sugar coating. But, it was a time consuming and expensive process. Application of sugar coating also resulted in significantly increasing the tablet weight, possibly affecting dissolution profiles.³

Various inert coating agents can be used to coat bitter drugs. They include starches, polyvinyl pyrrolidones (povidone) of various molecular weights, gelatin,

methylcellulose, hydroxyl methylcellulose, microcrystalline cellulose and ethyl cellulose. These coating agents simply provide a physical barrier over the drug particles. One of the most efficient methods of drug particle coating is the fluidized bed coating.

In this approach, powders as fine as 50 mm are fluidized in an expansion chamber by means of heat, high-velocity air, and the drug particles are coated with a coating solution introduced usually from the top as a spray



through a nozzle. Increasing the length of the coating cycle can increase coating thickness.

MICROENCAPSULATION

Microencapsulation is a process in which the active moiety (solid or liquid droplets) is coated with a polymeric material or film.^{5,6,11}

Types of microencapsulation include-

- Air suspension coating
- Co-acervation phase separation
- Spray drying

- Spray congealing
- Solvent evaporation
- Pan coating
- Interfacial polymerization, etc.

Of these processes, first four are mostly used techniques for achieving taste masking. Microencapsulation by co-acervation phase separation consists of three steps carried out under continuous agitation, such as: formation of three immiscible phases, deposition of coating and rigidization of coating.

Table 3: Microencapsulation¹⁹⁻²⁶

Author	Drug	Polymer	Result
Maccari <i>et.al</i>	Flucloxacillin	17% Ethyl cellulose	Flucloxacillin microencapsulated for taste abatement is as available from the tablet as the raw unprocessed antibiotic.
Cuna <i>et. al</i>	Cefuroxime Axetil	CAT, BP MCP-55 UPMCP 50	Microspheres represent a useful approach to mask its taste and assure its release in intestinal cavity.
Shen R.W <i>et. al</i>	Ibuprofen (air suspension coating)	Methacrylic acid copolymer	Chewable taste masked tablet having controlled release characteristics by fluid bed coating, obtained.
Sugao H <i>et.al</i>	Indeloxazine (fluidized bed with side spray method)	Hydrogenated oil and surfactant	Taste masking of drug without loss of bioavailability by heat treatment of wax coated microparticles.
Ozer AY <i>et.al</i>	Beclamide (simple co-acervation)	Gelatin, anhydrous sodium sulfate – coacervating agent	Core: wall ratio 1:1, microencapsulation to mask bitter taste.
Ishikawa T <i>et.al</i>	Oxybutynin HCl, pirenzepine HCl (extrusion method)	Eudragit E 100	Rapidly disintegrating tablets were prepared using prepared taste masked granules by compression method.
Shishu <i>et.al</i>	Ofloxacin (extrusion method)	Eudragit E 100	Taste masked granules were used for preparing rapidly disintegrating tablets and liquid oral suspension.
Al Omran <i>et.al</i>	Diclofenac sodium	Ethyl cellulose	Diclofenac sodium microcapsules were prepared using ethyl cellulose-toluene-petroleum ether, with solvent: nonsolvent ratio of 1:2.

Table 4: Spray Congealing²⁷

Author	Drug	Polymer	Result
Yajima <i>et. al</i>	Clarithromycin	Amino Alkyl Methacrylate Polymer E (AMCE)	Taste masking prevented by drug release in the mouth while ensuring rapid release in GIT.

Table 5: Solvent Evaporation Technique²⁸⁻²⁹

Author	Drug	Polymer	Result
Srikanth <i>et.al</i>	Drotaverine hydrochloride	Polymethylacrylic polymer	Polymethylacrylic polymer improves the unpleasant taste of orodispersible Drotaverine hydrochloride tablet.
V. Anand <i>et. al</i>	Prednisolone	Eudragit E 100	Drug polymer 1:10 microspheres of Prednisolone are tasteless, further used for formulation into ODT.

USE OF LIPOPROTEINS

Another way of masking the unpleasant taste of therapeutic agent is to entrap them into liposome (figure 3). For example, incorporating into a liposomal formulation prepared with egg phosphatidyl choline masked the bitter taste of chloroquine phosphate in HEPES (N-2-hydroxyethylpiperzine-N'- 2- ethane sulfonic acid) buffer at pH 7.2.³⁰

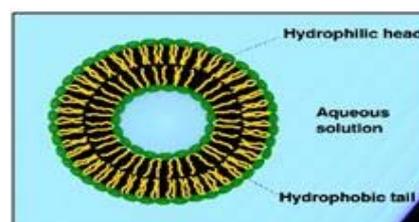


Figure 3

Table 6: Lipoprotein³¹⁻³²

Author	Drug	Polymer	Result
Katsuragi et.al	Quinine Propranolol	Lipoprotein composed of phosphatidic acid (PA) and Beta – Lactoglobulin (LG)	PA-LG effectively suppressed the bitter taste of the drugs.
Katsuragi et.al	Chloroquine phosphate	Egg phosphatidyl choline	Chloroquine phosphate was taste masked at pH 7.2 by incorporating into a liposomal formulation.

Table 7: Prodrug³³⁻³⁴

Author	Drug	Prodrug with improved taste
Taylor E.T et .al	Chloramphenicol	Palmitate ester
Hussain M et. al	NalbuphineHCl, Naltrexone, Naloxone, Oxymorphone HCL, Levallorphan	Esters of Nalbuphine, Naltrexone, Naloxone, Oxymorphone, Levallorphan

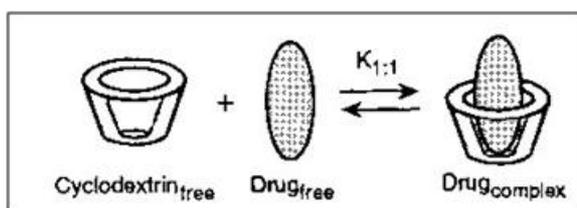
PRODRUG FORMATION

A prodrug is a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent drug.

e.g. 3-hydroxymorphinans are well absorbed from the buccal cavity, many of these compounds have a bitter taste which makes them difficult to administer by that route. The present invention relates to prodrugs of 3-hydroxymorphinans which are devoid of any taste, and are thus more suitable for buccal, sublingual, or nasal administration. Either rapid absorption or decline of plasma drug concentrations or prolonged plasma concentrations of active drug can be achieved by selecting prodrugs with appropriate solubility and hydrolysis rates. These can be formulated as tablets, gels, pastes, patches, or lozenges.

INCLUSION COMPLEX FORMATION

In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent i.e., the host molecule forming a stable complex (figure 4). The complexing agent is capable of masking the bitter taste of the drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds thereby reducing the perception of bitter taste. Vander Waals forces are mainly involved in inclusion complexes.^{3,12,35}

**Figure 4**

Cyclodextrins are widely used complexing agents for inclusion complex formation. Cyclodextrins are cyclic macromolecules obtained by degradation of starch by glycosyltransferases. Depending on the specific character of the respective transferases, different cyclodextrins results, consisting of 6 (alpha-cyclodextrin), 7 (beta-cyclodextrin), 8 (gamma-cyclodextrin) glucose units.

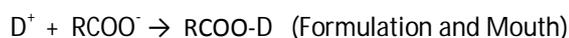
Beta-cyclodextrin is most widely used complexing agent for inclusion type complexes. It is sweet, nontoxic, cyclic oligosaccharide obtained from starch. The suppression of bitter taste by cyclodextrin was in increasing order of alpha, gamma, beta cyclodextrin.

USE OF ION EXCHANGE RESINS

Ion exchange resins are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium.¹¹

An ion exchange resin is an insoluble matrix (or support structure) normally in the form of small (1-2 mm diameter) beads, usually white or yellowish, fabricated from an organic polymer substrate. The material has highly developed structure of pores on the surface of which are sites with easily trapped and released ions. The trapping of ions takes place only with simultaneous releasing of other ions; thus the process is called ion exchange. There are multiple different types of ion exchange resin which are fabricated to selectively prefer one or several different types of ions.

A representation of the ion-exchange process showing the acid-base complex formed from a positively charged drug (D⁺) and a cation exchange resin (RCOO⁻).⁴



In taste masking by ion exchange resins, the resin-drug complexes formed will elute only a limited % of drug in the saliva pH. Thus the taste of the drug is masked without interrupting the drug release profile.^{5,8-10,11}

FORMATION OF MULTIPLE EMULSIONS

Multiple emulsions are also a good approach for taste masking of bitter drugs.

Multiple emulsions are polydispersed systems where both water in oil and oil in water emulsion exists simultaneously in a single system. Lipophilic and hydrophilic surfactants are used for stabilizing these two emulsions respectively. Multiple emulsions can be w₁/o/w₂ or o₁/w/o₂ depending on the dispersed phases in

dispersion media. These are called as emulsions of emulsions because one simple emulsion is placed inside another one.¹¹

Taste masking is achieved by dissolving the drug moiety in the inner aqueous phase of w/o/w emulsion with good shelf life stability. o/w/o emulsion is a type of multiple

emulsion in which water globules themselves containing dispersed oil globules, conversely w/o/w emulsions are those in which internal and external aqueous phases are separated by the oil.

Table 8: Inclusion Complexation³⁶⁻⁴²

Author	Drug	Polymer	Result
Shah P.et. al	Primaquine phosphate	Beta - cyclodextrin	Cachets prepared using physical mixture of drug and beta cyclodextrin in ratio of 1:25 showed complete bitter taste masking & easy redispersibility.
Stojanov M et. al	Cetirizine dihydrochloride	alpha - cyclodextrin, Beta – cyclodextrin and gamma- cyclodextrin	B – CD is only recommendable CD for taste masking oral pharmaceutical formulations.
Rajesh M.et. al	Cefuroxime Axetil	Beta - cyclodextrin	Inclusion complexation with BCD was found to be an excellent method in attaining palatability by masking undesirable taste of Cefuroxime Axetil.
Sheth S.K. et. al	Lornoxicam	Beta - cyclodextrin	Lornoxicam by complexing with beta cyclodextrin in 1:2 ratio by direct compression technique, masked the bitter taste of the drug.
Mate S. et. al	Duloxetine	Beta - cyclodextrin	Taste masking achieved by Hydroxy Propyl Beta-Cyclodextrin.
Soloman M. et. al	Ibuprofen aqueous solution	Hydroxypropyl Beta –Cyclodextrin	Taste masking was achieved by weight ratio of Ibuprofen: hydroxypropyl betacyclodextrin 1:11 to 1:15.
Patel et. al	Famotidine	HPMC	Taste masking due to complex formation with HPMC.

Table 9: Ion Exchange Resin⁴³⁻⁵³

Author	Drug	Polymer	Result
Patel <i>et.al</i>	Topiramate	Kyron T-114, kyron T-134, Doshion T-542	KyronT-114 with drug –resin of 1:3 was found to offer best taste masking.
Jena <i>et.al</i>	Ondansterone Hydrochloride	Indion 294	Indion 294 provides improved taste masking of Ondansterone Hydrochloride.
Suthar A.M <i>et .al</i>	Metronidazole	KyronT-114, Kyron T-134, Indion 234	Kyron T-134 at pH 8 showed potential to prepare palatable liquid formulation of Metronidazole.
Suthar A.M <i>et .al</i>	Tinidazole	KyronT-114, kyron T-134, Indion 234	kyronT-134 at pH 8 with Drug-resin ratio of 1:2 Gave best taste masked suspension of Tinidazole.
Mahore et. al	Metoclopramide HCL	Indion 234 (weak cation exchange resin)	Indion 234 (at low) pH 3 with drug resin ratio of 1:3, temperature of above 60°C gave 93.07% drug complexation showed best taste masking.
Saikat Das et. al	Ciprofloxacin	Indion 234	Indion 234 was used to mask bitter taste of drug.
Patra S et. al	Etoricoxib	Indion 204	Taste masking was achieved at drug resin ratio of 1:3.3
Bhise K et. al	Diphenhydramine HCL	Indion 234, Tulsion 343 (crosslinked polyacrylic backbone)	Effervescent and dispersible tablets developed from drug resin ratio of 1:2and 1:1. Successful taste masking with drug release of 95% in 15min was observed for effervescent and dispersible tablets.
Chaudhari P.D et. al	Rizatriptan benzoate	Indion 214	Drug release within 30 seconds, Indion 214 showed good results for taste masking.
Patel K. et .al	Fexofenadine HCl	Indion234	Use of Indion 234and Eudragit E100 offers taste masking with good flow properties and drug release.
Swapnil U. W et. al	Fexofenadine HCl	Doshion P547	Taste masking was achieved at drug:resin ratio 1:3, complete drug release was obtained at gastric pH in 2 hours.

SALT FORMATION

The salting-out taste-masking system is a multiparticulate system consisting of a drug core, a salting-out layer containing salts and water-soluble polymers, and a water-penetration control layer containing water-insoluble materials. The system generates a long lag time (time when released drug is less than 1%) for numbness

masking, and a subsequent immediate drug release for high bioavailability. Aiming to contain the system and drugs that cause numbness in oral disintegrating tablets, the system was optimized to reduce the particle size and contain drugs with high water solubility in this study. The amount of coating on the layers, the coating solvent, and the positioning of the components were also optimized.⁵⁴



Attempts were made to modify the chemical composition of the drug substance itself, so as to render it less soluble in saliva and thus make it less sensitive to the taste buds.

GRANULATION

Taste masking of a bitter taste drug can be masked by granulation process. Granulation is a major and common process in tablet production. In this approach, saliva insoluble polymers are used as binding agents in the tablet preparation. As these polymers are insoluble in saliva, thus the bitter taste of the drug can be masked. The taste masked granules can also be formulated as chewable tablet and rapidly disintegrating tablets EUDRAGIT® E polymers helps to seal sensitive actives and increase patient compliance by masking tastes and odors.⁵⁵

A schematic representation of the preparation procedure of the taste-masked granules is illustrated in Figure 5.^{12, 55,56}

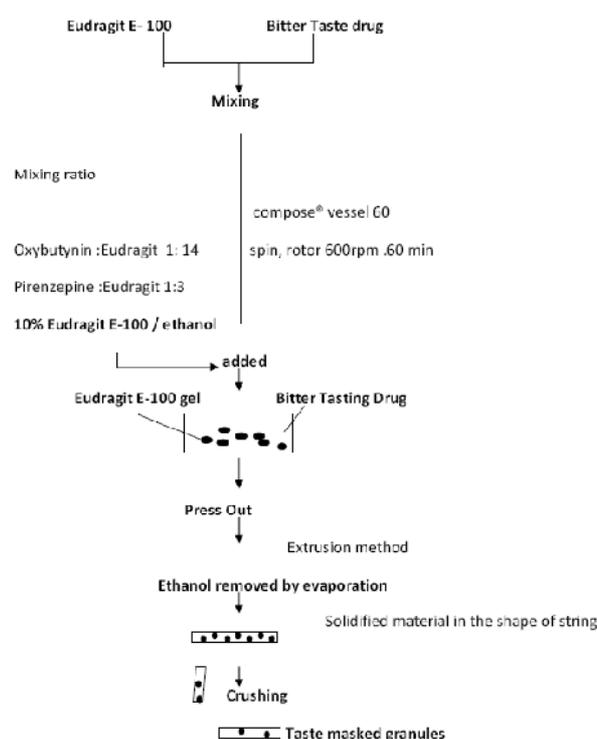


Figure 5

Table 10: Granulation⁵⁷⁻⁶¹

Author	Drug	Technique	Result
Tiwari S. B et. al	Tramadol HCL	Ethylcellulose coating, melt granulation	Ethylcellulose coating with water soluble excipients (HPMC 6 cps and lactose) proved to be useful as a functional coating to control drug release along with masking bitter taste.
Beatrice Albertini et. al	Acetaminophen	Wet granulation, steam granulation	Steam granulation techniques resulted for better taste masking without modifying the availability of the drug.
Kawano Y et. al	Furosemide	Wet granulation	Taste masking was achieved with yogurt powder when mixed in the ratio of furosemide: yogurt (1:1).
Sona P.S et . al	Diclofenac sodium	Wet granulation	Taste masked diclofenac sodium fast disintegrating tablets using veegum as taste masking agent (1:1.5) and sodium starch glycolate and croscarmellose sodium (5%) as superdisintegrants were successfully prepared.
Shakeel et.al	Norfloxacin Tinidazole	Ethyl Cellulose, HPMC	More acceptability than plain film coated tablet. Improved performance and acceptability.

EVALUATION OF TASTE MASKING EFFECT

Taste is a subjective perception, through taste buds located on the tongue. Each taste bud contains several taste cells, which can respond to a variety of taste sensations. Depending on individual, the perceived taste may vary to different degrees. By controlling the experimental conditions, reproducible results can be obtained.

To evaluate the taste sensation, following methods have been reported:

- By multichannel taste sensors.
- By flavor profile panel testing.
- By E-tongue.
- Measurement of frog taste nerve response.
- By spectrophotometric method

1) Multi channel taste sensors.⁶²

The taste sensor consists of three parts; 1) the electrode part consisting of the reference electrode and the artificial lipid/polymer film sensor which imitates lipid bilayer membranes, 2) the robot arm, and 3) the computer for data analysis.

When the electrode part is soaked in the sample solution, the lipid membrane potential is changed by the electrostatic interaction of the lipid film with the medicine that is measured, and/or by the adsorption of the medicine to the surface of the lipid film. The difference between the electric potential of the each working electrode and the reference electrode becomes the output, and these signals are sent to the computer through the robot arm as the "taste information"



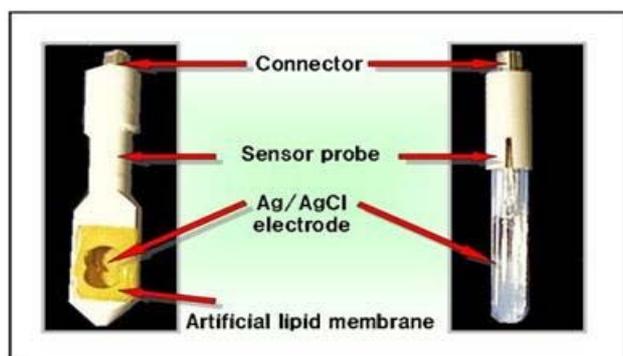


Figure 6

Figure 6 shows a typical multi channel taste sensor

2) Flavor Profile Panel Method.^{62,63}

The flavor profile is widely used descriptive analytical test. It is based on a natural process, often performed instinctively, for evaluating and comparing flavor. A flavor profile measures objectively, qualitatively the perceptible factors of a product that is aroma flavor by mouth, feeling factor and after use sensations. In the flavor profile method, a product flavor profile is created and refined with repeated panel sessions.

Aroma and flavor are assessed in terms of the following factors:

- Amplitude - overall impression of the aroma and flavor, integrating balance and body
- Perceptible aroma.
- Flavor.
- Taste character notes.
- Intensity of each character note.
- Order of appearance of each character note - larger differences in the time of appearance of notes are more apparent in unblended flavors.
- Aftertaste - flavor residue after the product has been completely swallowed.

3) E-tongue.⁶⁴

The electronic tongue is an instrument that measures and compares tastes. Chemical compounds responsible for taste are perceived by human taste receptors, and the seven sensors of electronic instruments detect the same dissolved organic and inorganic compounds. Like human receptors, each sensor has a spectrum of reactions different from the other. The information given by each sensor is complementary and the combination of all sensors results generates a unique fingerprint. Most of the detection thresholds of sensors are similar or better than those of human receptors. In the biological mechanism, taste signals are transduced by nerves in the brain into electric signals. E-tongue sensors process is similar: they generate electric signals as potentiometric variations.

How to perform an analysis with the E-Tongue

Liquid samples are directly analyzed without any preparation, whereas solids require a preliminary dissolution before measurement. Reference electrode and sensors are dipped in a beaker containing a test solution for 120 seconds. A potentiometric difference between each sensor and a reference electrode is measured and recorded by the E-Tongue software. These data represent the input for mathematical treatment that will deliver results.

Range of applications

- Electronic Tongues have several applications in various industrial areas: the pharmaceutical industry food and beverage sector, etc. It can be used to:
 - Analyze flavor ageing in beverages (for instance fruit juice, alcoholic or non alcoholic drinks, flavored milks...).
 - Quantify bitterness or "spicy level" of drinks or dissolved compounds (e.g. bitterness measurement and prediction of teas).
 - Quantify taste masking efficiency of formulations (tablets, syrups, powders, capsules, lozenges...).
 - Analyze medicines stability in terms of taste and benchmark target products.

4) Measurement of Frog Taste Nerve Response.⁶²

In this method, adult bullfrogs are anaesthetized intraperitoneally and the glossopharyngeal nerve is then identified and dissected from the surrounding tissue and cut proximally. An A.C. amplifier and an electronic integrator are used respectively to amplify and integrate the nerve impulse. The peak height of the integrated response is then taken as the magnitude of response. Quinine sulphate formulations, taste masked by PA-LG (phosphatidic acid-lactoglobulin) combination has been reported to be evaluated by this technique.

5) Spectrophotometric Method.⁶²

A known quantity of the supposedly taste masked formulation is mixed with 10 ml of distilled water in 10 ml injection syringe by revolving the syringe, end to end 5 times in 30 seconds. The test medium is then filtered through a membrane filter, followed by spectrophotometric determination of the concentration of drug in the filtrate. If this concentration is below the threshold concentration it may be calculated that the bitter taste would be masked in vivo. This technique has been applied to evaluate the taste upto 100 µg/ml.

6) Sensory analysis.⁶⁵

Sensor analysis employs objective or analytical methods and subjective methods.

A. Subjective Methods**1. Preference Test**

- a. Paired Testing
- b. Triangle Testing

2. Hedonic scale**B. Objective Methods****1. Difference Test**

- a. Paired Difference Test
- b. Triangle Difference Test
- c. Duo-trio Test.

2. Ranking Test**C. Analytical**

- a. Time-Intensity Test
- b. Single Attribute Test
- c. Flavour profile
- d. Dilution profile
- e. Statistical test

COMMERCIALY AVAILABLE TASTE MASKING TECHNOLOGIES

Oral pharmaceuticals often impart an unpleasant taste, primarily bitterness. The desire for improved palatability in these products has prompted the development of numerous methods for taste masking, such as complexation of the drug with resins or cyclodextrins, use of microcapsules, particle coating, etc. Many of these contributions have been successfully commercialized in oral pharmaceutical preparations that are available over the counter or by prescription.

1. KV Pharmaceuticals has developed a number of taste-masked technologies, including Flavortech, a liquid formulation technology designed to reduce the bad taste of therapeutic products.⁶⁶

2. Micromask is a taste-masking technology that incorporates a dry-powder, microparticulate approach to reduce objectionable taste by sequestering the unpleasant drug agent in a specialized matrix.⁶⁶

MicroMask® coating technology can be applied to over-the-counter and prescription drugs to yield products that exhibit superior taste- and odor-masking, and mouth-feel characteristics. Additionally, it can be operated at a moderate temperature, which reduces the potential of thermal degradation of the active ingredient. MicroMask® products are particularly noted for their ability to meet dissolution and bioavailability requirements, while maintaining their taste- and odor- masking characteristics. MicroMask® products exhibit excellent flow and compression characteristics. Flow is critical in tableting operations to ensure that no blockages or

bridging occur. MicroMask® products help to ensure high machine efficiency. The pliable coating of MicroMask® particles affords excellent tableting characteristics and reduces the compression force required to produce an acceptable tablet. These factors reduce tool wear and lower the cost to produce tablets using MicroMask® products.⁶⁷

3. Liquette is a taste-masking technology that incorporates unpleasant tasting drugs into a hydrophilic and lipophilic polymer matrix to suppress the taste.⁶⁶

4. Oraquick is a technology in which the bitter taste of a drug candidate is first enhanced by neutralizing its negative taste characteristics and then developed into a quick-dissolving tablet formulation.⁶⁶

FUTURE PROSPECTS IN TASTE MASKING

Various formulations have been examined for the development of taste-masked oral pharmaceuticals in recent years. Especially many efforts have been made in the development of oral fast-disintegrating tablets, and dry syrup and liquid products which can inhibit bitter taste, for use in oral dosage forms for a wide array of drugs taken by infants or elderly patients.⁶⁸⁻⁷⁰

In order to develop more desirable and palatable taste-masked formulations, taste altering with flavors, like sweeteners, could be conducted in conjunction with taste masking by physical methods.

To date, the most widely used method for measuring the taste characteristics of pharmaceutical preparations is psychophysical evaluation by a taste panel. However, conventional chemical analyses, on the basis of release studies, have been shown to be useful subsidiary methods. More recently, novel in vitro taste assessment apparatus and methodologies have been developed for high-throughput taste screening and quality control. Biomimetic taste sensing systems (BMTSSs), such as multichannel taste sensors or electronic tongues with global selectivity, have been welcomed by both pharmaceutical scientists and the industry as a whole.

Established and effective taste-masking approaches used to formulate APIs in syrups and soft-chew dosage forms can be applied to APIs in the thin film oral dosage format

Taste-masking nanotechnology can be used to mask unpleasant tastes in pharmaceuticals and nutraceutical preparations, vastly improving consumer acceptance, patient compliance and user satisfaction. The Nanolipidic particles used in this study are safe and all-natural, marking the first successful testing of an all-natural integrated delivery system in taste-masking applications. Further benefits of using these proprietary Nanolipidic particles in taste-masking includes the high-loading capacity of passenger molecules, an optically clear appearance, the ability to control population size, a 60 nm to 150 nm range and a system that is inherently non-precipitating.



CONCLUSION

Taste masking of a bitter drug has been a challenge to scientists. The approaches discussed here with not only mask the bitter taste of the drug but also enhance the solubility, onset of action or bioavailability of the drug. With application of these techniques and proper evaluation of taste masking effect one can improve product preference to a large extent. In addition to oral drug delivery, the taste masked drug delivery research is gaining importance for the quality of the treatment provided to patients, especially children and old.

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