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Taste Masking: A Novel Approach for Bitter and Obnoxious Drugs

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ABSTRACT:

Taste is an important parameter in case of drugs administering orally. Taste masking becomes a prerequisite for bitter drugs to improve the patient compliance especially in the pediatric and geriatric population. The problem of bitter taste of drug in pediatric formulations is a challenge to the formulators in the present scenario. Masking the bitter taste of drugs is a potential tool for the improvement of patient compliance which intern decides the commercial success of the product. Two approaches are commonly utilized to overcome the bad taste of the drug. The first includes reduction of drug solubility in the saliva and second approach is to alter the ability of the drug to interact with taste receptor. Various methods are available to mask the undesirable taste of the drugs. Some of them are coating of drug particles, by formation of inclusion complexes, molecular complexes of drugs with other chemicals, solid dispersions, melting method, micro encapsulation, prodrugs, mass extrusion methods and ion exchange resins.

KEYWORDS: Bitter drugs, Taste masking, Sense of taste, Taste masking techniques.

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INTRODUCTION: ⁽¹⁻⁴⁾

Taste is one of the most important parameters governing patient compliance. Undesirable taste is one of several important formulation problems that are encountered with certain drugs. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients. Several oral pharmaceuticals, numerous food and beverage products, and bulking agents have unpleasant, bitter-tasting components. So, any pharmaceutical formulation with a pleasing taste would definitely be preferred over a competitor's product and would translate into better compliance and therapeutic value for the patient and more business and profits for the company. The desire of improved palatability in these products has prompted the development of numerous formulations with improved performance and acceptability.

The sense of taste

Taste is the ability to respond to dissolved molecules and ions—"gatekeeper to the body". Human detects taste with taste receptor cells that are clustered in to onion-shaped organs called taste buds. Each taste bud has a pore that opens out to surface of the tongue enabling molecules and ions taken into the mouth to reach the receptor cells inside. Diagram of taste bud is given in figure 1.

Human have around 10,000 taste buds which appear in fetus at about three months. A single taste bud contains 50-100 taste cells. Each taste cells receptors on its apical surface. These are transmembrane proteins which bind to the molecules and ions that give rise to the four primary taste sensations namely - salty, sour, sweet and bitter.

Recently, a fifth basic taste umami has been discovered. The umami is the taste of

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certain amino acids (e.g. monosodium glutamate). There is often correlation between the chemical structure of a compound and its taste. Low molecular weight salts tend to taste salty where as high molecular weight salts tend toward bitterness. Nitrogen containing compounds, such as alkaloids, tend to be quite bitter. Organic compounds containing hydroxyl groups tend to become increasingly sweet as numbers of OH group increase. Four basic tastes are confirmed to specific regions of tongue (Table1).

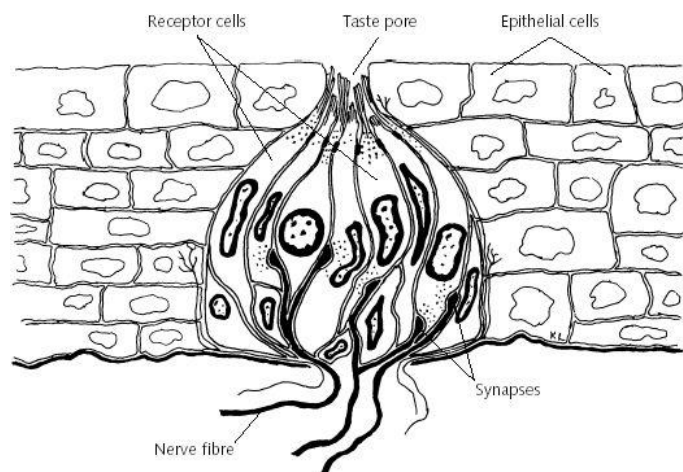


Figure 1. A taste bud

The methods most commonly involved for achieving taste masking include various chemical and physical methods that prevent the drug substance from interaction with taste buds. The simplest method involves use of flavor enhancers. Where these methods fail more complex methodologies are adopted. Various techniques have been identified for taste masking which include polymer coating, inclusion complex formation with cyclodextrin, use of ion exchange resins, solubility limiting methods, liposome, multiple emulsions, use of anesthetic agents, etc. An ideal taste masking process and formulation should have the following properties. ^[6]

- 1) Involve least number of equipments and processing steps.
- 2) Require minimum number of excipients for an optimum formulation.
- 3) No adverse effect on drug bioavailability.
- 4) Require excipients that are economical and easily available.
- 5) Least manufacturing cost.
- 6) Can be carried out at room temperature.
- 7) Require excipients that have high margin of safety.
- 8) Rapid and easy to prepare.

Factors that are taken into consideration during the taste-masking formulation process include: ⁽⁷⁾

- 1) Extent of the bitter taste of the API.
- 2) Required dose load.
- 3) Drug particulate shape and size distribution.
- 4) Drug solubility and ionic characteristics.
- 5) Required disintegration and dissolution rate of the finished product.

- 6) Desired bioavailability.
- 7) Desired release profile
- 8) Required dosage form

Taste masking techniques

1. Taste masking with sweeteners and flavours ⁽⁸⁾

(A)Flavors

Natural Flavors

- Juices - Raspberry
- Extracts - Liquorices
- Spirits - Lemon & Orange
- Syrups – Blackcurrant
- Tinctures -Ginger
- Aromatic waters - Anise & Cinnamon
- Aromatic Oils – Peppermint & Lemon.

Synthetic Flavors

- Alcoholic solutions
- Aqueous solutions
- Powders

Natural Vs Synthetic

- Cheaper
- More readily available
- Less variable in chemical composition
- More stable

Basis of Choosing a Flavor

- Complementary to existing flavor of the drug
- Known popularity of particular flavors
- Age of patients
- Allergy

Flavoring agents for taste masking

Basic Taste	Masking agents
Salt	Butterscotch, maple, apricot, peach, vanilla, wintergreen mint.
Bitter	Wild cherry, walnut, chocolate, mint, anise.
Sweet	Vanilla, fruit and berry.
Sour	Citrus flavor, licorice, root beer, raspberry.

(B) SWEETNERS

- Complement flavors associated with sweetness
- Soothing effect on the membranes of the throat

Natural Sweetener

- Sucrose, glucose, fructose
- Sorbitol, mannitol, glycerol
- Honey, liquorice

Artificial sweetener

- Saccharin, Saccharin sodium
- Aspartame

Nutritive: Sucrose, Fructose and Glucose

Polys: Mannitol, Sorbitol, Xylitol, Erythritol, Maltitol.

Non-Nutritive: Aspartame, Sucralose, Neotame and Saccharine

Novel sweeteners: Trehalose, Tagatose

List of FDA approved Non-Nutritive Sweeteners

(Sweetness factor, Sucrose = 1)

Sr.no	Sweetner	Sweetness factor
1	Aspartem	180-200
2	Sucralose	600
3	Acesulfame K	200
4	Neotame	7000-13000
5	Saccharin	300

2. Taste masking by granulation: ⁽⁹⁾

Granulation is a less expensive, rapid operation and an easily scalable taste masking technology. This step can be exploited as a mean for taste masking of slightly bitter tasting drug. Granulation lowers the effective surface area of the bitter substance that come in contact with the tongue upon oral intake. Liquid and low melting point waxes such as glycerol palmitostearate, glyceryl behenate and hydrogenated castor oil are commonly used ingredients during the granulation to achieve taste masking.

3. Taste masking by Microencapsulation: ⁽¹⁰⁾

Microencapsulation is a process by which very tiny droplets or particles of liquid or solid material are surrounded or coated with a film or polymeric material. Coating is an extremely useful technique for a number of applications in pharmaceutical field. Although it is used primarily for production of sustained release, Gastro-intestinal dosage forms, it also has major applications in masking the unpleasant taste. It is important to understand that only soluble portion of the drug can generate the sensation of taste. Coating the active drug with a properly selected polymer film can reduce its solubility in saliva and thus taste could be masked. Coating the drug particles created a physical barrier between the drug and the taste buds and taste of active could be masked. The goal of Microencapsulation may be accomplished by any of the following techniques.

- Air suspension coating
- Coacervation - phase separation
- Spray drying and spray congealing
- Solvent evaporation
- Multiorifice - centrifugal process
- Pan coating
- Interfacial polymerization

Polymers used for coating in Microencapsulation ⁽¹¹⁻¹³⁾

Coating is an extremely useful technique for number of applications in the pharmaceutical field. It is classified based

on the type of coating material, coating solvent system, and the number of coating layers. By coordinating the right type of coating material it is possible to completely mask the taste of a bitter drug, while at the same time, not adversely affecting the intended drug release profile. Polymers have been exclusively used as coating materials, either alone or in combination, as a single or multi-layer coat, in the taste masking of bitter medicaments. Combinations of pH independent water insoluble polymers such as cellulose ethers, cellulose ester, polyvinyl acetate and water soluble polymers such as cellulose acetate butyrate, polyvinylpyrrolidone, hydroxyethyl cellulose have been used to attain a balance between the taste masking and in vitro release.

Hydrophobic polymers have been popularly used for coating bitter medicaments to achieve taste masking. These coating agents simply provide a physical barrier over the drug particles. However, hydrophilic polymers may also provide taste masking of Ibuprofen, by coating with hydrophilic polymers such as hydroxyethyl cellulose or a mixture of hydroxyethyl cellulose and hydroxypropyl methylcellulose. Sweeteners can be included in the coating solution for a better taste masking performance. One of the most efficient methods of drug particle coating is the fluidized bed processor. In this approach powder as fine as 50µm, are fluidized in expansion chamber by means of heated, high velocity air and the drug particles are coated with a coating solution introduced usually from the top as spray through nozzle. The coated granules are dried with warm air.

4. Ion Exchange Resins: ⁽¹⁴⁾

Ion exchange resins (IER) have received considerable attention from pharmaceutical scientists because of their versatile properties as drug delivery vehicles. In past few years, IER have been extensively studied in the development of Novel drug delivery system and other biomedical applications. Several ion exchange resin products for oral and peroral administration have been developed for immediate release and sustained release purposes. Bitter tasting drugs can be absorbed onto ion exchange resins, thus effectively removing them from solution during the transit through the mouth, at salivary pH 6.8, remains in intact form making the drug unavailable for the taste sensation. Various studies have revealed that ion exchange resins are equally suitable for drug delivery technology. Some ion exchange resins used widely for taste masking purpose in industries are Amberlite IRP64, Amberlite IRP69, Indion 204, Indion 214, Kyron T-114 and Kyron T-104.

5. Taste masking by formulation of inclusion complexes: ⁽¹⁵⁾

Inclusion complexation is a process in which the guest molecule is included in the cavity of a host or complexing agent. The complexing agent is capable of masking bitter taste of drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste

buds. Cyclodextrin is most widely used complexing agent for inclusion type complexes. It is sweet, non toxic, cyclic oligosaccharide obtained from starch. The following are the examples of drugs that the bitter taste can be suppressed by making inclusion complexes.

6. Taste masking by Prodrug approach: ⁽¹⁶⁾

Chemical modification, including prodrug design is an effective method for reducing solubility, and thereby improving taste. A prodrug is chemically modified inert drug precursor which upon biotransformation liberates the pharmaceutically active parent compound. Bitterness of a molecule may be due to the efficiency of the taste receptor substrate adsorption reaction, which is related to the molecular geometry of the substrate. If alteration of the parent molecule occurs by derivative formation, the geometry is altered, affecting the adsorption constant. Thus the magnitude of a bitter taste response or taste receptor-substrate adsorption constant may be modified by changing the molecular configuration of the parent molecule. The extremely bitter antibiotics have been the focus of much work in reversible drug modification. Taste masking of drug by Prodrug approach is given in table 2.

7. Solid dispersion system: ⁽¹⁶⁻¹⁷⁾

Solid dispersion has been defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting (fusion) solvent or melting solvent method. Recently solid dispersions were introduced as a taste masking technology. Tsau and Damani (1994) disclosed a drug-polymer matrix composition to achieve the taste masking of dimenhydrinate. Amine or amido group of dimenhydrinate can have a physical and chemical interaction with the carboxylic acid and esters groups of copolymers such as shellac, zein and cellulose acetate phthalate hydrophobic polymers and long chain fatty acids have been used to achieve the taste masking by solid dispersion. This approach usually requires a higher concentration of excipients compared to other taste masking techniques. Natural polymers such as shellac and zein, and enteric polymers like derivatives of acrylic acid polymers and phthalate are good choices to develop the taste masked solid dispersions.

8. pH Modifiers: ^(18,19)

Many natural and synthetic polymers, resins and waxes alone or in combination have been employed for taste masking. The enteric polymers like eudragit L are used for taste masking but the pH of saliva is near 5.8 and these polymers solubilize at pH beyond 5.5 so there is a possibility of drug being partially leached. Therefore there is a need for the development of taste masking polymer such that the bitter taste is completely masked by the polymer at the pH of saliva in mouth and in the reconstitution medium as in case of the liquid orals and further which is able to protect the drug in a biologically active form, from the moisture in the dosage form and releasing the drug rapidly in the stomach without affecting its absorption and bioavailability.

9. Taste masking by adsorption: ^(20, 21)

Adsorbates are commonly used in taste masking technologies. Adsorbate of bitter tasting drug can be considered as the less saliva soluble versions of these drugs. Adsorption involves preparing a solution of the drug and mixing it with an insoluble powder that will adsorb the drug, removing the solvent, drying the resultant powder, and then using these dried adsorbates in the preparation of the final dosage form. Many substrates like veegum, bentonite, silica gel and silicates can be used for the reparation of adsorbate of bitter drugs. The bitter taste of ranitidine is masked by forming an adsorbate with a synthetic cation exchange resin.

10. Taste masking by gelation: ⁽²²⁾

Water insoluble gelation on the surface of tablet containing bitter drug can be used for taste masking. Sodium alginate has the ability to cause water insoluble gelation in presence of bivalent metal ions. Tablet of amiprololose hydrochloride have been taste masked by applying a undercoat of sodium alginate and overcoat of calcium gluconate. In presence of saliva, sodium alginate reacts with bivalent calcium and form water insoluble gel and thus taste masking achieved.

11. Multiple Emulsions: ^(23, 24)

A novel technique for taste masking of drugs employing multiple emulsions has been prepared by dissolving drug in the inner aqueous phase of w/o/w emulsion under conditions of good shelf stability. The formulation is designed to release the drug through the oil phase in the presence of gastrointestinal fluid.

12. Development of Liposome: ⁽²⁵⁾

Another way of masking the unpleasant taste of therapeutic agent is to entrap them into liposome. 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.

13. Miscellaneous taste masking approaches:

• By effervescent agents ^(26, 27)

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have been employed for use as taste masking agents for dosage forms that are not dissolved in water prior to administration. A chewing gum composition of bitter medicament was formulated to supply the medicament to oral cavity for local application or for buccal absorption. It comprise a chewing base, an orally administrable medicament, a taste masking generator of carbon dioxide, and optionally a taste bud desensitizing composition (e.g., oral anesthetic such as benzocaine) and other non active material such as sweeteners, flavoring components, and fillers. Recently, effervescent tablets of fentanyl and prochlorperazine were

developed to supply these drugs to the oral cavity for buccal, sublingual, and gingival absorption. The formulation contains the drug in combination with effervescent agent to promote their absorption in the oral cavity and to mask their bitter taste. An additional pH adjusting substance was also included in fentanyl formulation for further promotion for absorption.

• **Rheological modification** ^(28,29)

Increasing the viscosity with rheological modifier such as gums or carbohydrates can lower the diffusion of bitter substances from the saliva to the taste buds. Acetaminophen suspension can be formulated with xanthan gum (0.1-0.2%) and microcrystalline cellulose (0.6-1%) to reduce bitter taste. The antidepressant drug mirtazapine is formulated as an aqueous suspension using methonine (stabilizer) and maltitol (thickening agent). Maltitol is stable in the acidic pH range of 2 to 3 and besides masking the unpleasant taste of the drug, it also inhibit its undesirable local anesthetic effect .

• **Continuous multipurpose melt (CMT) Technology** ⁽³⁰⁾

The CMT method was developed for the continuous granulation and coating of pharmacologically active substances. It was concluded that this method could be successfully applied for taste masking of bitter drugs. All the details regarding taste masking products given in table.3.

EVALUATION TECHNIQUES

Sensory evaluation

Taste, to think of, is a very subjective perception. Depending on individuals, the perceived taste may vary to different degrees. If we have well controlled experimental set up, it is possible to accurately and reproducibly measure taste thresholds. To quantitatively evaluate taste sensation, following methods have been reported in Literature.

- a. Panel testing (human subjects)
- b. Measurement of frog taste nerve responses.
- c. Multichannel taste sensor/ magic tongue
- d. Spectrophotometric evaluation/ D30's value

a. Panel Testing ⁽³¹⁾

The panel testing is a psychophysical rating of the gustatory stimuli. In this method, a group of about 5-10 human volunteers is trained for taste evaluation by using reference solutions ranging in taste from tasteless to very bitter. Numerical values are then assigned to these levels of bitterness (e.g. 0-5). Subsequently, test solution is tasted and rated on the same scale to assess its bitterness. Literature reports panel testing in invariably all the taste-masked drugs being evaluated.

b. Measurement of Frog Taste Nerve Responses ⁽³²⁾

In this method, adult bull frogs are anaesthetized intraperitoneally and the glossopharyngeal nerve is then

located and dissected from the surrounding tissue and cut proximally. An ac-amplifier and an electronic integrator are used to respectively amplify and integrate the nerve impulses. The peak height of the integrated response is then taken as the magnitude of response.

c. Multichannel Taste Sensor / Magic tongue ⁽³³⁾

This is an automated taste sensing device to detect the magnitude of bitterness of a drug substance. The device has a transducer which is composed of several kinds of lipid/polymer membranes with different characteristics that can detect taste in a manner similar to human gustatory sensation. Taste response is transferred into a pattern composed of electric signals of membrane potentials of the receptor part. Different response electric potential pattern are obtained for substance producing different taste qualities.

Recently, the technique has been applied, for the quantitative evaluation of the bitterness of some commercially available medicines. Quinine hydrochloride was taken as the standard for bitterness.

d. Spectrophotometric Method ⁽³⁴⁾

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

Table 1: Specific area of tongue and threshold concentration for primary taste sensations ⁽⁵⁾

Taste Concentration	Area of tongue	Threshold
Sweet(sucrose)	Tip of tongue	0.5%
Salt(NaCl)	Tip and sides of tongue	0.25%
Sour(HCl)	Sides of tongue	0.007%
Bitter(Quinine)	Back of tongue	0.00005%

Table 2. Taste masking of drug by Prodrug approach ⁽¹⁷⁾

Parent Drug	Pro-drug with improved taste
Clindamycin	Alkyl ester
Chloramphenicol	Palmitate or phosphate ester
Erythromycin	Alkyl ester
Lincomycin	Phosphate or alkyl ester
Tetracyclin	3,4,5-Trimethoxy benzoate salts

TABLE 3: LIST OF DRUG, EXCIPIENTS AND TECHNIQUES USED FOR THE PREPARATION OF TASTE MASKED PRODUCT.

DRUG	TECHNIQUE	EXCIPIENTS	REFERENCE
Eucalyptus oil	flavors and sweeteners	Fenchone, borneol	35
Ibuprofen	flavors and sweeteners	Saccharin sodium sucrose, sorbitol solution	36,37
Acetaminophen	Microencapsulation Wurster fluid bed coating	Crosscarmellose	38
Dextromethorphan hydrobromide	Top spray fluid bed coating	PVP-K30	39
Theophylline	Tangential spray fluid bed coating	Eudragit NE30D, guar gum	40
Ampicillin trihydrate	Spray drying	Sodium CMC	41
Nizatidine	Spray drying	Eudragit E-100	42
Ciprofloxacin	ion exchange resins	Lewatit CNP	43
Dextromethorphan hydrobromide	ion exchange resins	Carbomer 934	44
Ephedrine hydrochloride	ion exchange resins	Indion CRP 244/254	45
Erythromycin	ion exchange resins	Carbomer 934	46
Orbifloxacin	ion exchange resins	Amberlite IRP64/69	47
Paroxetine HCL	ion exchange resins	Amberlite IRP88	48
Benexate hydrochloride	Complexation	Cyclodextrin	49
Chloroquine phosphate	Complexation	Tannic acid	50
Dimenhydrinate	Complexation	Eudragit S-100	51
Gymnema sylvestra	Complexation	Chitosan	52
Ibuprofen	Complexation	Hydroxypropyl- β cyclodextrin	53
Poly lactic acid	Multiple emulsion	NaCl, CaCl ₂ , Brilliant blue dye	54

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