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Review Article

# Taste Masking Techniques: An Updated Review

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**ABSTRACT**

Taste masking becomes a prerequisite for bitter drugs to improve the patient compliance especially in the pediatric and geriatric populations. Some orally administered drugs exhibit bitter taste. Two approaches are commonly utilized to overcome the bitter 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 receptors. Various methods are available to mask the undesirable taste of the drugs. Conventional taste masking techniques such as the use of sweeteners, amino acids and flavoring agents alone are often inadequate in masking the taste of highly bitter drugs. The recent techniques of taste masking are dispersion coating, granulation, solid dispersions, inclusion complexation, ion exchange resin approach, mass extrusions technique, spray drying, microencapsulation, liposomes, prodrugs, salt formation, adsorption, wet spherical agglomeration**s,** multiple emulsions, gel formation, effervescent technique and continuous multipurpose melt (CMT) technology. The field of taste masking of active pharmaceutical ingredients (API) has been continuously evolving with varied technologies and new excipients.



## INTRODUCTION

Taste is an important factor in the development of a dosage form. Tastes can be categorised into five primary taste qualities: sweet, sour, salty, bitter, and umami or savory. Within hours after birth, the infants reject bitter tastes and prefer sweet and umami tastes [1]. Children have a much greater number of taste buds than adults which are responsible for sensitivity towards taste. These taste buds regenerate every two weeks. As with many of the senses, taste becomes altered as a function of the aging process, which explains why most children find certain flavors to be too 'strong' when adults do not [1].

Undesirable taste is one of the 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 have unpleasant bitter tasting components. To overcome this problem several techniques are evolved to mask the bitter taste of drugs.

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These techniques not only serve to mask the taste of a drug but also enhance the bioavailability of drug dosage forms. Commonly used techniques that are adopted for large scale production of pharmaceutical dosage forms are use of flavors and sweetener, coating of drug particles with inert materials, formation of inclusion complexes, ion exchange resin approach, spray drying, microencapsulation, liposomes, prodrugs, adsorption, multiple emulsions and formation of molecular complexes of drug with other chemicals [1].

### Taste Buds

Taste buds are small sense organs in most vertebrates, helps in the detection of taste. Hence there are a group of cells, found especially on the tongue. Taste buds have been identified on the soft palate, pharynx, epiglottis, which allow different types of tastes to be recognized [1].

#### *Salty taste (edge and upper portion):*

The salty taste is one among the five taste receptors of the tongue. They are located on the edge and upper front portion of the tongue [1, 2].

***Sweet taste (tip):***
The sweet taste is one among the four taste receptors in the tongue. They are found on the tip of the tongue [1, 2].

***Sour taste (along sides in back):***
The sour taste is also one of the four taste receptors of the tongue. They occur at sides of the tongue and are stimulated mainly by acids.

***Bitter taste (back):***
The bitter taste is the last and one of the four taste receptors in the tongue. It is located towards the back of the tongue. It is stimulated by a variety of chemical substances, most of which are organic compounds, although some inorganic compounds such as magnesium and calcium also produce bitter sensations [1, 2].

**Factors affecting the taste-masking formulation process:**
Several factors affecting the taste masking formulation process are the 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 and required dosage form [2].

**Working of taste buds:**
Taste buds work by transmitting information about different kinds of tastes to brain via nerve fibers. Taste buds for all four types of tastes i.e. sweet, sour, salty and bitter shows distinct distribution patterns on the surface of human tongue. Taste buds have been identified on the soft palate, pharynx and epiglottis. The tongue, soft palate and epiglottis contain taste buds that allow human to recognize different tastes in food a they eat. The taste buds are chemo-receptors, meaning that they transmit chemical signals in food into electrical signals. These signals travel to the brain via nervous system to experience sensation of taste. It is to be noted that taste buds in fishes are distributed over the entire surface of the body to provide information about surroundings [3-6].

**Effect of age on taste buds:**
Cells that make up the taste buds wear out with age, as a result taste buds begin to disappear from roof and the sides of the mouth except taste buds that's are located over tongue. The remaining taste buds become less sensitive. Researchers have been proved that smoking and eating of scalding food may damage the taste buds. This lacking of taste may lead to loss of appetite and poor nutrition. Taste is a type of medium to experience the world of tastes for infants and young children. It is seen that children are more sensitive to certain tastes than any adults. The mechanism that causes taste sensitivity in youngsters is difficult to analyze[3,4].

**Methods to test taste buds:**
To conduct this experiment, we require food color. With the help of cotton, put food color over tip of your tongue. Put reinforcement ring over tongue. Start counting of pink dots inside the ring by using magnifying glass. These pink dots are fungi form papillae. These are having property of not to take up the food coloring. These papillae are tiny bumps like on our tongue i.e. house your taste buds more the number of papillae means more the sensitivity against the taste. If any person having less than 15 papillae on average is called as non-taster whiles those having more than 30 are called as supertasters **[3, 4]**.

**Taste-masking techniques:**
An ideal taste masking process and formulation should have the following properties like involve least number of equipments and processing steps, require minimum number of excipients for an optimum formulation, no adverse effect on drug bioavailability, require excipients that are economical and easily available, least manufacturing cost, can be carried out at room temperature, require excipients that have high margin of safety and easy to prepare **[5]**.
Various methods are available to mask undesirable taste of the drugs. Some of them are given below.

**Taste masking with flavors and sweeteners**
Masking of bitter taste by sweeteners is the simple approach. But this approach is not very successful for highly bitter drugs. Sweeteners and flavors are generally being used along with other taste masking techniques to improve the efficiency of these techniques. Cooling effect of certain flavoring agents' aid in reducing perception of bitterness **[6]**. There are a wide range of alternative sweeteners in the market today. Table 1 presents a compilation of the most common artificial and natural sweeteners used in pharmaceutical products and their relative sweetness levels. Synthetic sweeteners such as aspartame and sucralose are commonly used in

most taste masked products. Recently, sweeteners of plant sources such as stevia and glycyrrhizin have emerged as a viable alternative to the artificial sweeteners.

**Coating of drugs using a suitable polymer:**
Various inert coating agents can be used to coat bitter drugs. These coating agents simply provide a physical barrier over the drug particles. Various inert coating agents like starch; povidone, gelatin, methylcellulose, ethyl cellulose etc. are used for coating drug particles. One of the most efficient methods of drug particle coating is the fluidized bed processor. In this approach, powders as fine as 50 um are fluidized in an 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 a spray through a nozzle. Increasing the duration of the coating cycle can increase coating thickness. Taste masking of Ibuprofen has been successfully achieved by this technique to form microcapsules [7, 8].

**Taste masking by granulation:**
Granulation is a less expensive, rapid operation and an easily scalable taste masking technology. This step can be exploited as a means for taste masking of slightly bitter tasting drug. Granulation lowers the effective surface area of the bitter substance that comes in contact with the tongue upon oral intake. Liquids and low melting point waxes such as glycerol palmito stearate, glyceryl behenate and hydrogenated castor oil are commonly used ingredients (Table 2) during the granulation to achieve taste masking **[9, 10]**.

**Solid dispersion:**
Solid dispersion has been defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by fusion or solvent evaporation method. Carriers used in solid dispersion system include povidone, polyethylene glycol of various molecular weights, hydroxy propyl methyl cellulose, urea, mannitol and ethyl cellulose. Various approaches for preparation of solid dispersion are described below [11].

***Melting method***: In this method, the drug or drug mixture and carrier are melted together by heating. The melted mixture is cooled and solidified rapidly in an ice bath with vigorous stirring. The final solid mass is crushed and pulverized.

***Solvent method***: In this method, the active drug and carrier are dissolved in a common solvent, followed by solvent evaporation and recovery of the solid dispersion.

***Melting solvent method*:** In this method, drug in solution is incorporated into molten mass of polyethylene glycol at a temperature 70°C without removing the solvent.

**Inclusion complexation:**
In this process, the drug molecule fits into the cavity of a complexing agent forming a stable complex. The complexing agent is capable of masking the bitter taste of a 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. The inclusion complexes with cyclodextrin owing their existence to van-der Waals forces between the host and guest **[11]**. Cyclodextrin is the most widely used complexing agent for inclusion type complexes. It is a sweet, nontoxic and cyclic oligosaccharide derived from starch. Cyclodextrin forms inclusion complexes with organic molecules both in solid state and in solution [12].

**Ion-exchange resins (IERS):**
Ion exchange resins are synthetic inert organic polymers consisting of a hydrocarbon network to which ionisable groups are attached and they have the ability to exchange their labile ions for ions present in the solution with which they are in contact. The most frequently employed polymeric network used is a copolymer of styrene and divinyl benzene (DVB). Apart from this other polymers such as those of acrylic and methacrylic acid cross linked with DVB and containing appropriate functional groups, have been used as ion exchange drug carriers [13].

**Mass extrusion:**
This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets [14, 15].

**Table 1:** Relative sweetness of commonly used sweeteners

| Sweetening agent | Relative sweetness | Remarks |
|---|---|---|
| **Natural sugar substitutes** | | |
| Curculin | 550 | Exhibits taste-modifying activity |
| Glycyrrhizin | 50 | Moderately expensive |
| Lactose | 0.16 | Large amount required |
| Mannitol | 0.60 | Negative heat of solution |
| Stevia | 250 | Negligible effect on blood glucose |
| **Artificial sugar substitutes** | | |
| Acesulfame potassium | 137-200 | Bitter after taste if used in higher concentration |
| Alitame | 2,000 | Pending FDA Approval |
| Aspartame | 200 | Not very stable in solution |
| Cyclamate | 40 | Banned due to its carcinogenic effect |
| Neotame | 8000 | Heat stable and extremely potent and safe |
| Neohesperidin dihydrochalcone | 1500 | Artificial bitterness suppressor and flavor modifier |
| Saccharin | 300 | Unpleasant after taste |
| Sucralose | 600 | Synergestic sweetening effect |

* Sucrose is taken as a standard of 1 for comparison.

**Table 2:** Taste masking of drug by granulation

| Granulating agent(s) | Drug(s) | Percentage of excipients | Comments |
|---|---|---|---|
| Alginic acid | Erythromycin | Drug : polymer ratio of 2.5:1 to 50:1 | Taste masked granules, which can be formulated as dry syrup suspensions / chewable or dispersible tablets |
| Cyclodextrin | Dextromethorphan | Drug: polymer ratio of between 0.9:1 and 1:25 | Mixing of drug with cyclodextrin followed by granulation; without complexation |
| Microcrystalline cellulose (MCC) | Ibuprofen | Ratio of drug to MCC is 70:30 to 90:10 w/w | A simpler and more effective process compared to coating |

**Spray drying technique:**

In this technique, bitter taste of drug is masked by preparing microparticles of drug with certain hydrophilic polymers such as hydroxyl propyl methylcellulose (HPMC) and poly vinyl pyrrolidone (PVP) by using spray drying technique. The purpose of this technique is to develop the taste masked microspheres of intensely bitter drug by spray drying technique. By use of different polymers, microspheres are formed and it is found that the taste masking capacity and drug release profile are excellent. The microspheres are characterized by Fourier transform infrared spectroscopy, scanning electron microscopy, drug loading, *in vitro* bitter taste evaluation, and drug release properties [16-19].

**Microencapsulation technique:**

Microencapsulation is a process of applying relatively thin coating to small particles of solid, droplets of liquid and dispersion. This is the method being widely used in Pharma industries to mask the taste of bitter drugs as well as to achieve better bioavailability. Coating agents employed in microencapsulation are gelatin, povidone, HPMC, ethyl cellulose, carnauba wax, acrylics and shellac. In this method, bitter drugs are first encapsulated to give free flowing microcapsules which are then blended with excipients and compressed into tablets. Methods used to prepare microencapsules are air suspension, coacervation, phase separation, spray drying and cngealing, pan coating, solvent

evaporation and multiorifice centrifugation method [20, 21].

**Development of liposomes:**

Another way of masking the unpleasant taste of therapeutic agent is to entrap them into liposomes. In this, taste maskings with lipophilic vehicles used are lipids, lecithin and lecithin like substances. Acetaminophen granules are sprayed with molten stearyl stearate, mixed with suitable tablet excipients, and incorporated into a taste masked, chewable tablet formulation. Formulations with a large excess of lecithin or lecithin-like substances are claimed to control bitter taste in pharmaceuticals. Magnesium aluminum silicate with soybean lecithin is used to mask the unpleasant taste of talampicillin HCl [22, 23].

**Prodrug approach:**

The alkyloxyalkyl carbonates of the clarithromycin 2' position have remarkably alleviated bitterness and improved bioavailability when administered orally. Tasteless/bitterless prodrugs of opioid analgesics and antagonists were formulated for improved buccal delivery. Tasteless prodrugs of nalbuphine HCl, naltrexone, naloxone, oxymorphone HCl, butorphanonol, and levallorphan were synthesized for buccal administration to improve bioavailability relative to that of oral dosing without the characteristic bitter taste. In rats, the prodrugs demonstrated up to 90% bioavailability. It was concluded that when administered as prodrugs, bioavailability improved without visible adverse effects [24-27].

**Salt preparation:**

Adding alkaline metal bicarbonate such as sodium bicarbonate masks the unpleasant taste of water-soluble ibuprofen salts in aqueous solution. The bitter taste of caffeine may be masked by formulating it as a carbonated oral solid preparation using sodium bicarbonate, ascorbic acid, citric acid, and tartaric acid. Magnesium aspirin tablets are rendered tasteless by preparing magnesium salts of aspirin. Penicillin prepared as N, N' dibenzylethylene-diamine diacetate salts or N,N'-bis (deyhdroabiety) ethylenediamine salts is tasteless**.** Bitterness-reduced antitussive and expectorant compositions (tablets) of dihydrocodeine phosphate, DL methylephedrine HCl, and D-chlorpheniramine maleate contain magnesium salts, sweeteners, starch, and cellulose [25, 26].

**Adsorption:**

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 final dosage form. Many substances like veegum, bentonite, silica gel and silicates can be used for the preparation of adsorbate of bitter drugs. Loperamide and phenyl propanolamine have been adsorbed on magnesium aluminium silicates also known as veegum F to prepare bitter taste masked suspension of these drugs [28].

**Wet spherical agglomeration (WSA):**

Technique and Continuous Multipurpose Melt (CMT) Technology. A novel microencapsulation process combined with the wet spherical agglomeration (WSA) technique was used to mask the bitter taste of enoxacin. The microcapsules prepared were bio-equivalent to the commercial Enoxacin 100 mg tablets in beagle dogs. 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 [26].

**Multiple emulsions:**

A novel technique for taste masking of drugs employing multiple emulsions has been prepared by dissolving the 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 [27].

**Gel formation:**

Water insoluble gelations 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. Tablets of amiprolose hydrochloride have been taste masked by applying an undercoat of sodium alginate and overcoat of calcium gluconate. In presence of saliva, sodium alginate reacts with bivalent calcium and forms

water insoluble gel and thus taste masking achieved [27].

**Miscellaneous methods:**

***Effervescent agents*:**

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have also 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(s) was formulated to supply the medicament(s) to the oral cavity for local application or for buccal absorption. It comprises a chewing gum base, an orally administrable medicament, a taste masking generator of carbon dioxide, and optionally a taste bud desensitizing composition (e.g., oral anesthetics such as benzocaine and spilanthol) and other nonactive materials, 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 formulations contain the drugs in combination with effervescent agent(s) 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 of absorption [28].

***Continuous multipurpose melt (CMT) technology*:**

The CMT 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 drug [29, 30].

**Taste masking by rheological modifications:**

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. This provides a taste masked liquid preparation for administration of a relatively large amount of unpleasant tasting medicines.

The composition of such a formulation comprises a taste-masking liquid base with a high viscosity induced by thickening agent such as polyethylene glycol and sodium carboxy methyl cellulose. Surprisingly, it has been observed that the high viscosity liquid excipient base provides taste masking benefits to such an extent that extra strength compositions can be prepared with high concentration of bitter tasting ingredients. For example, guaifensine, which is normally administered in doses of not more than 100 mg in 5 ml of liquid, may be administered in doses of 200 mg/5ml, without the feel of bitter taste [31].

**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, the following methods have been reported in the literature: Panel testing (human subjects), Measurement of frog taste nerve responses, Multichannel taste sensor/ magic tongue and Spectrophotometric evaluation/ D30's value.

***Panel testing*:**

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, the test solution is tasted and rated on the same scale to assess its bitterness. Literature reports, panel testing in invariably all the taste-masked frugs being evaluated. The ease of the method combined with the accuracy of human perception of taste against any other gustatory evaluation technique makes panel testing the most commonly used Technique [32].

***Measurement of Frog Taste Nerve Responses*:**

In this method, adult bull frogs are anaesthetized intraperitoneally and the glossopharyngeal nerve is then located and dissected from the surrounding tissues 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.

Quinine sulphate formulations, taste masked by PA-LG (phosphatidic acid-lactoglobulin) combination has been reported to be evaluated by this technique [33, 34].

***Multichannel Taste Sensor / Magic tongue*:**
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 patterns are obtained for substances producing different taste qualities [35]. 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. Basic drugs with amino groups in the molecule such as quinine show a comparatively good correlation between the relative response electric potential (mV) of channels 1 or 2 of the taste sensor, which contain negatively charged membranes, and the bitterness as determined by human gustatory sensations tests. Secondly, for anionic drugs, such as diclofenac sodium or salicylic acid, the positively charged membrane in channel 5 or 6 seemed to be useful even through them are being sour rather than bitter. For drugs with both an amino (cationic) group and a carboxylic acid (anionic) group in the molecule, such as theophylline, caffeine and metronidazole, the electric potential (mV) of channel 1 or 2 did not increase, even though bitterness was observed in human gustatory sensation test. Therefore, different types of membrane components will be needed for a complete evaluation of the bitterness of medicines [35].

***Spectrophotometric method*:**
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 evalute the taste masked granules of sparfloxacin, with threshold concentration being 100µg/ml [36, 37].

## CONCLUSION
The above study helps us to develop the taste mask active pharmaceutical active ingredients for development of advanced dosage forms for more patient convenience. Further study is required to select best taste masking technique among all the techniques mentioned above by conducting various researches. Thus taste masking techniques puts a greater challenge to make the pharmaceutical dosage form more economic.

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