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### An update of taste masking methods and evaluation techniques

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#### ABSTRACT

*Taste is an important factor in the development of dosage form. Many orally administered drugs elicit bitter taste. Palatability is an extremely important factor in ensuring the likelihood that the recipient will take medicine. Previously the attitude of “Worse the taste of medicine, better the cure” was observed, but now-a-days several approaches of masking the bitter taste have been developed. It includes adding sugars, flavors, sweeteners, use of lipoproteins, numbing taste buds, coating drug, microencapsulation, multiple emulsion, viscosity modifier, vesicles and liposomes, prodrug and salt formation, inclusion and molecular complexes, solid dispersion, application of Ion Exchange Resins (IERS). This article reviews the earlier methodologies and approaches of taste masking and bitterness reduction.*

**Keywords:** Taste masking, taste abatement, Electronic Tongue, E-tongue, Microencapsulation.

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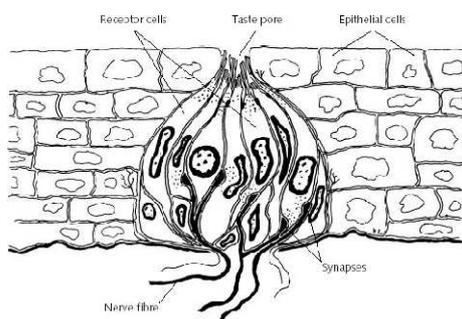
#### INTRODUCTION

Taste is one of the most important parameter 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 have unpleasant bitter tasting components. The desire of improved palatability in these products has prompted the development of numerous formulations with improved performance and acceptability<sup>[1,2]</sup>. To study various techniques of taste masking the basic information regarding taste sensation need to be understood.

**The sense of taste:**

Taste is the ability to respond to dissolved molecules and ions “gatekeeper to the body”<sup>[3,4]</sup>. 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 tongue enabling molecules and ions taken into the mouth to reach the receptor cells inside<sup>[5]</sup>.

Human have around 10,000 taste buds which appear in fetus at about three months. A single taste bud contain 50-100 taste cells. 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<sup>[6]</sup>.(Fig.1)



**Fig:1 Taste buds**[5,6]

Recently, a fifth basic taste umami has been discovered. The umami is the taste of certain amino acids<sup>[6,7]</sup>. There is often correlation between the chemical structure of 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 number of OH group increases<sup>[5]</sup>. Receptor mechanism involves initial depolarization at apical receptor site, which causes local action potential in receptor cell. This in turn causes synaptic activation of the primary sensory neuron. Four basic taste are confirmed to specific regions of tongue (Table 1). But some workers deny the presence of specific regions of the tongue for a particular taste and consider it as a misconception<sup>[8]</sup>.

Threshold for taste is a minimum concentration of a substance that evokes perception of taste. The following table 1 gives the threshold concentration of four primary taste sensation.

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

**Table 1. specific area of tongue and threshold concentration for primary taste sensations**[8]

It can be seen that tongue is 10,000 times more sensitive to the bitterness of quinine than to sweetness of sugar. Saccharine, on this scale would rate about 0.001%<sup>[5]</sup>. Pharmaceutical companies can save themselves much grief by addressing the taste factor early in the product development. In so doing, they can get their medications to market more quickly, ensure patient

compliance, gain market leadership and reap generous economic rewards. They can also stay in compliance with FDA's final rule, which went into effect December 2000<sup>[9]</sup>.

So major taste masking efforts are required before bitter drugs are acceptable for market trials. Major taste masking technologies are based on the reduction of solubility of the drug in the saliva so the drug concentration in saliva will remain below taste threshold value. The desire for improved palatability of formulations has prompted the development of various new technologies for taste abatement. Many of these technologies have been successfully commercialized. But, the ideal solution of taste masking would be the discovery of universal inhibitor of bitter taste of all drug.

### **Taste masking techniques:**

To achieve the goal of taste abatement of bitter or unpleasant taste of drug. Various techniques reported in the literature are as follows

1. Addition of flavoring and sweetening agents.
2. Microencapsulation.
3. Ion exchange resins.
4. Inclusion complexes.
5. Granulation.
6. Adsorption.
7. Prodrug approach.
8. Bitterness inhibitors.
9. Multiple emulsions.
10. Solid dispersion.
11. Molecular complexes.
12. Gel formation.
13. Use of liposomes.
14. Mass extrusion method.
15. Use of salt and derivative.
16. Use of amino acids and protein hydrates.
17. Miscellaneous.

#### **1. Taste masking with flavors and sweeteners:**

This techniques is simplest approach for taste masking. But this approach is not very successful for highly bitter drugs. Artificial sweeteners and flavors are generally being used alone with other taste-masking techniques to improve the efficiency of these techniques[10,11].

Eucalyptus oil is a major constituent of many mouth washes and cough drops formulation which is a bitter tasting substance. Its bitter taste can be masked by agent including fenchone, borneol or isoborneol<sup>[12]</sup>.

Cooling effect of certain flavoring agent aids in reduction perception of bitterness. The physiology involved is merely to numb taste buds, either rapidly or over a period of time, so that the cooling effect actually build up after ingestion. The brain perception the coolness even though physically the temperature of the product has not changed<sup>[13]</sup>.

Some generalization concerning the selection of flavors to mask specific types of taste have been suggested by Janovasky and Wesley<sup>[14]</sup>. Such recommendations are listed in table 2.

**Table 2. Flavor selection[41,14]**

Taste sensation	Recommended flavor
Salt	Butterscotch, apple, peach, vanilla
Bitter	Wild cherry, walnut, chocolate, mint
Sweet	Fruit and berry, vanilla
sour	Citrus flavor, licorice, root beer, raspberry

A combination of flavoring agents is usually employed. Flavor adjuvants like menthol and chloroform are considered as desensitizing agents because addition to their own odor or a flavor they also have a mild anesthetic effect on taste receptors. Aspirin medicated floss contains sodium phenolate as an anaesthetizing agent in addition to chocolate flavor to mask the bitter taste of aspirin<sup>[15]</sup>. A survey of the taste preferences of human race, as a whole, indicates that sweet taste is very agreeable to our species. Hence for controlling the taste qualities effort is directed to make the preparation sweet to different degrees. Sweeteners are commonly used for this purpose. Aspartame is used as a prominent sweetener in providing bitterness reduction<sup>[16]</sup>. A very small concentration (0.8%) is effective in reducing bitterness of 25% acetaminophen. Cyclamates have been banned by the USFDA since 1970 due to its carcinogenic effect.

The neohesperidine dihydrochalcone is an artificial bitterness suppressor and flavor modifier. It is an open chain analogue of neohesperidine, a bitter flavanone that occurs in Seville oranges (*Citrus Aurantium*). It is a bitterness suppressor and flavor modifier that also elicits a very intense lingering sweet taste. Due to its lingering sweet taste the taste of a bitter substance appears later in time and taste could be masked<sup>[17,18]</sup>.

## 2. Microencapsulation:

It is important to understand that only the soluble portion of a drug can generate the sensation of taste, and it is possible, or even likely, that coating the active drug with a properly selected polymer film can reduce its solubility in saliva and taste could be masked. Coating the drug particles creates a physical barrier between the drug and the taste buds and this taste of active could be masked. Microencapsules are made up of a polymeric skin or wall enclosing a core<sup>[19,20]</sup>. 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<sup>[5]</sup>. The goal of microencapsulation may be accomplished by any of the following techniques<sup>[14]</sup>:

1. Air suspension coating
2. Coacervation-phase separation
3. Spray drying and spray congealing
4. Solvent evaporation
5. Multiorifice-centrifugal process.
6. Pan coating
7. Interfacial polymerization.

In literature first four techniques of microencapsulation have been reported for taste masking purpose, as shown in table 3. The air suspension coating process can appropriately be described as a upward moving, expanded, fluidized bed in central portion of the coating chamber coupled with a downward-moving, more condensed fluidized bed on the periphery of the column. Three types of air suspension coater are available, namely, top spray coater, wurster bottom spray coater and tangential spray coater<sup>[21]</sup>.

### **3. Polymers used for coating:**

One of the most important factor to be considered in taste masking by coating is selection of coating polymers. Ideally, the coating polymers should be such that it prevents the release of active agent in the oral cavity, following per oral intake, but allows it in stomach or small intestine where the drug is expected to be absorbed. Polymers, which mainly insoluble at salivary pH 6.8 but readily, dissolves at gastric pH 1.2 could be a good candidate for taste masking. Choosing one of these polymers is not a simple selection. Before making a decision on coating material following factors must be considered. The particle size of drug, flow characteristics of drug, moisture sensitivity, long term stability, temperature of processing and most important, method delivery of active drug molecule<sup>[35,36,37]</sup>. Cushioning material like Avicel pH102, microcrystalline cellulose (MCC), can reduce the rupturing of microcapsule if used as direct compressible diluents<sup>[38]</sup>.

Once the type of coating and the plasticizers (if any) to use have been established then level of coating has to be optimized. If purpose of coating is taste masking, it may be simple taste panel to determine the proper coating level. Thick coating can cause problems both in terms of size and cost apart from being problematic in getting the desired release profile of the drug. However, by coordinating the right type of coating material. It is possible to completely mask the taste of bitter drug while at the same time, not adversely affecting the intended drug release profile. Various coating materials for taste masking reported in literature are different grades of Eudragit<sup>[24,25,26,27,28,29,33,39]</sup>, cellulose materials<sup>[22,24,25,27,28,30]</sup> and waxes<sup>[33,35,40]</sup> formulations.

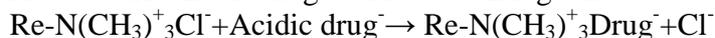
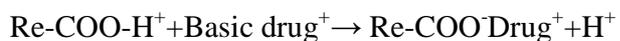
### **4. Taste masking by ion exchange resins:**

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<sup>[5]</sup>. The most frequently employed polymeric network used is a copolymer of styrene and divinylbenzene (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.<sup>[42,43]</sup>

#### **Types of resins (table 4)**

IERs contain positively or negatively charged functional group and are thus classified as either anionic or cationic exchangers. Within each category, they are classified as strong or weak, depending on their affinity for capable counter ions. These insoluble IERs may be supplied in case of cation exchangers as sodium, potassium or ammonium salt and of anion exchangers usually as the chloride. It is frequently necessary to convert a resin completely from one ionic form to another. Charged drugs are normally loaded on to IERs by two methods like column and

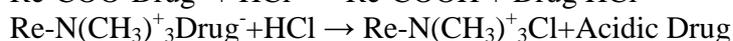
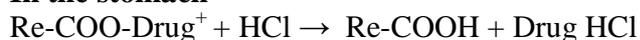
batch method<sup>[42,46]</sup>. The reaction involved during complexation of drug with resin may be indicated as follows<sup>[49]</sup>



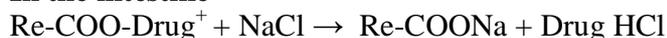
Upon ingestion, drugs are most likely eluted from cation exchange resins by  $\text{H}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$  ions and from anion exchange resins by  $\text{Cl}^-$ , as these ions are most plentiful available in gastrointestinal secretions.

Typical reactions involved in the gastrointestinal fluids may be envisaged as follows:

#### **In the stomach**



#### **In the intestine**



#### **Exchange capacity**

The exchange capacity of IERs refers to the number of ionic sites per unit weight or volume (meq./gram or meq./mL). Sulfonic acid resin derived from polystyrene matrix have lower exchange capacities, about 4 meq/gms, than carboxylic acid resins derived from acrylic acid polymer, about 10 meq/gms, because of bulkier ionic substituent of sulfonic acid resin and polystyrene matrix<sup>[44]</sup>.

Weak acid cation exchange resin have pKa value of about 6, so that pH4 or above their exchange capacity tends to increase. Ionization of weak acid cation exchange resin occurs to appreciable extent only in alkaline solution, i.e. in their salt form. This is reported that their exchange capacity is very low below pH 7 and moderately constant values at pH above about 9.

The rate of ion exchange is influenced by the permeability of the solvent and solute through the pores of the resin, whose number and size are influenced by the amount of crosslinking. The diffusion path length is obviously also related to the size of the resin particles<sup>[42,46]</sup>.

#### **Applications:**

IERs are used in drug formulation to stabilize the sensitive components<sup>[47]</sup>, sustain release of the drug, and taste masking<sup>[48-52,95]</sup>. Interaction of amine drugs with polycarboxylic acid IERs indicated that these resins may be quite useful in taste coverage<sup>[57-63]</sup>. These studies indicated that saliva with an average pH of 6.7 and a cation concentration of 40 meq/L, would only elute a limited percentage of drug from adsorbate. However rapid elution would occur as soon as the adsorbates is exposed to the low pH of the stomach. The particle coating of polycarboxylic acid IER adsorbates can also be considered as a method for achieving taste coverage. This is beneficial because the taste coverage ability of the uncoated adsorbate<sup>[5]</sup>.

**5. Taste masking by formulation of inclusion complexes:**

Inclusion complexes are 'host-guest' relationship in which complexing agent act as host and provide cavities in which foreign guest molecule may fit. Cyclodextrin form inclusion types of complexes with organic molecules both in solid state and in solution<sup>[64]</sup>. 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, thereby reducing the perception of bitter taste. Vander-walls forces are mainly involved in inclusion complexes.  $\beta$ -cyclodextrins is most widely used complexing agent for inclusion type of complexes. It is sweet, non-toxic, cyclic oligosaccharide obtained from starch. Carbapentane citrate can be formulated in palatable liquid formulation with 50% reduced bitterness by forming 1:1 complex with cyclodextrin. Similarly a 1:11 to 1:15 inclusion complex of ibuprofen and hydroxyl propyl- $\beta$ -cyclodextrin can be formulated as palatable solution<sup>[65]</sup>. Bitter amine drugs such as chloroquine phosphate can be treated with tannic acid for taste abatement purpose<sup>[66]</sup>. Bitter taste of dimenhydrinate can be masked by forming a porous drug-polymer matrix with a copolymer having a plurality of carboxylic acid and ester groups, example Eudragit S-100<sup>[5]</sup>.

**6. Taste masking by granulation:**

Granulation is a common processing step in the production of tablet dosage form. This step can be exploited as a mean for taste masking of slightly bitter tasting drug. Some saliva insoluble polymers can also act as binding agent, granules prepared from these polymers show less solubility in saliva and thus taste could be masked. Granulation lowers the effective surface area of the bitter substance that comes in contact with the tongue upon oral intake. But this reduction in surface area of bitter substance may or may not be effective in masking the bad taste. Taste masked granules, prepared from saliva insoluble polymer, can be formulated in various type of tablet dosage form. example rapidly disintegrating tablets and chewable tablets<sup>[67]</sup>. Taste masked granules of bitter tasting drug pirenzepine and oxybutynin have been prepared by the extrusion using aminoalkyl methacrylate copolymer. (EudragitE-100)<sup>[68]</sup>.

**7. Taste masking by 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 substance 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<sup>[69]</sup>.

**8. Prodrug approach:**

A prodrug is chemically modified inert drug precursor which upon biotransformation liberates the pharmaceutically active parent compound. A combination of factors is perhaps operative in the demonstration of a taste response molecular geometry is one of them for example, 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. This effect, in turn, may or may not be due to lack of aqueous solubility of the derivative to eliminate the bitter taste response. 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 (table 5)<sup>[2,41,70,73]</sup>.

**Table 5: Prodrug for bitter taste masking**<sup>[71,72,73]</sup>

Parent molecule	Reversible modification
Chloramphenicol	Palmitate or phosphate ester
Clindamycin	Alkyl ester
Erythromycin	Alkyl ester
Lincomycin	Phosphate or alkyl ester
Tetracycline	3,4,5-trimethoxy benzoate salts

### 9. Solid dispersion system<sup>[2,5,41]</sup>:

Solid dispersion have 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. Carriers used in solid dispersion system includes Povidone, Polyethylene Glycol of various molecular weights, Hydroxy Propyl Methyl Cellulose, Urea, Mannitol and Ethyl Cellulose<sup>[94]</sup>. Various approaches for preparation of solid dispersion are described below:

#### 1. 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.

#### 2. 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.

#### 3. Melting solvent method<sup>[64]</sup>:

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

### 10. Molecular complexes of drug with other chemicals:

The solubility and adsorption of drug can be modified by formation of molecular complexes. Consequently lowering drug solubility through molecular complex formation can decrease the intensity of bitterness of drug Higuchi and Pitman, reported that caffeine forms complexes with organic acids that are less soluble than xanthan and as such can be used to decrease the bitter taste of caffeine<sup>[5,64,93]</sup>.

### 11. Use of bitterness inhibitor:

The development of a specific universal inhibitor for bitter taste has been widely required in the fields of taste physiology and pharmaceutical sciences, but no such inhibitors has been available. One difficulty in discovering of universal inhibitor for bitter taste is that substances that inhibit bitterness of one compound will not influence the bitterness of a second because many different classes of compound impart bitterness<sup>[5]</sup>.

### 12. Taste masking by gelation:

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 amiprolse hydrochloride have been taste masked by applying an undercoat of sodium alginate and overcoat of calcium gluconate. In presence of saliva, sodium alginate react with bivalent calcium and form water insoluble gel and thus taste masking achieved<sup>[74]</sup>.

### **13. Use of multiple emulsion<sup>[75-92]</sup>:**

A novel technique of taste masking of drug employing multiple emulsion. The w/o/w or o/w/o type multiple emulsion are vesicular systems in which active ingredients can be entrapped in internal phase. The entrapped substances can be transferred from internal phase to external phase through the membrane phase. This phase controls the release of drug from system. These system could be used for controlled-release delivery of pharmaceuticals. If the system is stable enough for a reasonable shelf life, the formulation could also mask the taste of drug<sup>[75]</sup>. Both w/o/w or o/w/o multiple emulsion of chloroquine phosphate have been prepared and reported to be partially effective in masking the bitter taste of drug<sup>[76]</sup>.

### **14. Use of liposomes:**

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 phosphotydydyl choline masked the bitter taste of chloroquine phosphate in HEPES (N-2-Hydroxyethylpiperazine-N'-2)-ethane sulfonic acid) buffer at pH 7.2<sup>[90]</sup>. Bitter substances are commonly hydrophobic in nature hence lipoprotein composed of phosphatidic acid and  $\beta$ -lactoglobulin can mask the target sites for bitter substances on the taste receptor membrane without affecting responses to salts, acids, sugars or sweet amino acids<sup>[5]</sup>. Selective inhibition of bitter taste of various drugs by phospholipids such as phosphatidic acid, phosphatidylinositol, soy lecithin, have been reported. Bitter taste of polymyxin B sulfate and trimethoprim-sulfamethoxazole have been masked by BMI 60 obtained by fractionating soy lecithin<sup>[78]</sup>.

### **15. Use of salts or derivatives:**

In this approach, an attempt is made to modify the chemical composition of the drug substance itself, so as to the taste buds. Aspirin tablets can be rendered tasteless by making magnesium salt of aspirin. D-chlorpheniramine maleate is taste-masked salt of chlorpheniramine. The alkyloxy alkyl Carbonates of Clarithromycin have remarkably viated bitterness and improved bioavailability when administered<sup>[65]</sup>. Sodium salts such as sodium chloride, sodium acetate, sodium gluconate have been shown to be potent inhibitors of some bitter compound. The mechanism is not known, however, research shows that sodium act at peripheral taste level rather than a cognitive effect<sup>[79,80]</sup>.

### **16. Use of amino acids and protein hydrates:**

By combining amino acids or their salts with bitter drugs, it is possible to substantially reduce the bitterness. Some of the preferred amino acids include sarcosine, alanine, taurine, glutamic acid, and glycine. The taste of ampicillin improved markedly by preparing its granules with glycine and mixing them with additional quantity of glycine, sweeteners, flavors and finally compressing them into tablets<sup>[91]</sup>.

### **17. Mass extrusion method:**

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. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste<sup>[2,5,90]</sup>.

### **18. Miscellaneous methods:**

#### **A. By effervescent agents**

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 chewable gum composition of bitter medicament was formulated to supply the medicament to oral cavity for local application or 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 example oral anesthetics such as benzocaine and other non active material such as sweeteners, flavoring components and fillers<sup>[81]</sup>. 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<sup>[82]</sup>.

#### **B. Rheological modification:**

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/ 5 ml, without the feel of bitter taste<sup>[41,84]</sup>.

#### **C. 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<sup>[5,67]</sup>.

### **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 measures taste thresholds. To quantitatively evaluate taste sensation, following methods have been reported in literature<sup>[5,41]</sup>.

#### **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 solution ranging in

taste from tasteless to very bitter. Numerical values are then assigned to these levels of bitterness like 0-5. Subsequently, test solution is tasted and rated on the same scale to assess its bitterness<sup>[5,41,85]</sup>.

**Table 6: Evaluation of taste masking<sup>[41]</sup>**

Subjective method	Objective method
Preference test	Difference test
Paired test	Paired difference test
Triangle test	Triangle difference test
Hedonic scale	Duo trio test, single attribute test
	Ranking test, dilution test
	Analytical test, statistical test
	Flavor profile, time intensity test

Frog test nerve responses: In this method, adult bull frog is 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 responses is then taken as the magnitude of response<sup>[5,86]</sup>.

#### **Electronic tongue:**

This is an automated taste sensing device to detect the magnitude of bitterness of 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 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 substances producing different taste qualities<sup>[5,41,87,96]</sup>. 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 drug 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<sup>[88]</sup>.

#### **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*.<sup>[5]</sup> This technique has been applied to evaluate the taste masked granules of sparfloxacin, with threshold concentration being 100 µg/ml<sup>[89]</sup>. Generally the taste evaluation involves the objective or analytical method and subjective or hedonic method.

### **CONCLUSION**

We have made an attempt to describe various methods, which could be suitable for taste masking of bitter drugs. The methods described in this review can be used for bench scale as well as pilot scale also. There are numbers of technologies available, which effectively mask the

objectionable taste of drugs but require skillful application, which does not affect the bioavailability of drug. With application of these techniques and proper evaluation of taste masking effect one can improve product preference to a large extent. Moreover, the development of taste masking methodology requires great technical skill, and the need for massive experimentation.

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