TASTE MASKING TECHNOLOGIES: A NOVEL APPROACH FOR THE IMPROVEMENT OF ORGANOLEPTIC PROPERTY OF PHARMACEUTICAL ACTIVE SUBSTANCE

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ABSTRACT
Acceptability of any dosage form are mainly depends over its taste i.e. mouth feel. Drug molecule interacts with taste receptor on the tongue to give bitter, sweet or salty taste sensation, when they dissolve in saliva. This sensation of the taste is the result of signal transduction from the receptor organs for taste, commonly known as taste buds. In market, there are numbers of pharmaceutical preparations available in which actives are bitter in taste. The improved palatability in these products has prompted the development of numerous formulations, which improved performance and acceptability. The bitterness of preparation also leads to patient incompliance. To overcome this problem, many techniques have been developed to mask the bitter taste of drugs. These techniques are not only mask the bitter taste of drug but also enhance the bioavailability and performance of drug dosage form. It includes adding sugars, flavors, sweeteners, use of lipoproteins, numbing taste buds, granulation, use of adsorbats, coating drug, microencapsulation, multiple emulsion, viscosity modifier, vesicles and liposomes, prodrug and salt formation, inclusion and molecular complexes, solid dispersion and Ion Exchange Resins (IERs) which have been tried by the formulators to mask the unpleasant taste of the bitter drugs. The present review article highlights different technologies of taste masking with respect to dosage form and novel methods of evaluation of taste masking effect.

Keywords: Taste, Taste masking, Bitter drugs, Taste buds, Taste masking technology, Evaluation.

INTRODUCTION
Organoletic properties are important considerations for development of a solid oral dosage form that can influence consumer preference and compliance. In the case of bitter drugs, taste is one of the most important parameter governing patient compliance and oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers especially for pediatric and geriatric.

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. To study various techniques of taste masking the basic information regarding taste sensation need to be understood.

Physiology of Taste
The sense of taste is mediated by taste bud, which are group of taste receptor cell (50 – 100 cells), bundled together in clusters like bananas and gives sensation of taste via sensory neurons to central nervous system (CNS) in the brainstem(Fig. 1). Taste buds are chemoreceptor stimulated by chemicals dissolved in saliva from oral ingested medicaments and enter via the taste pore followed by interaction with surface proteins known as taste receptors causing electrical changes within taste cells, which cause the transmission of signals to the brain.

Four fundamental sensations of taste have been described

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<th>Salty taste (edge, upper portion)</th>
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<td>The salty taste is one among the four taste receptors of tongue. They are located on the edge and upper front portion of the tongue.</td>
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<th>Sweet taste (tip)</th>
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<td>The sweet taste is one among the four taste receptors in the tongue. They are found on the tip of the tongue.</td>
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<th>Sour taste (along sides in back)</th>
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<td>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.</td>
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Bitter taste (back)
The bitter taste is the last and one of the four taste receptors in the tongue. That is located toward 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.

Taste Signaling Pathways
Taste transduction begins with the interaction of a tastant (e.g. medicine or food) with taste receptor cells in the taste buds(Fig. 2). The taste buds with G-Protein coupled receptors (GPCRS) in the cells triggering the release the release of G-Protein called Gustducin. The process of taste sensation begins when Gustducin activates the effector enzymes phosphodiesterase IA (PDE) or phospholipase C beta-2(PLC). The effector enzyme then changes the intracellular level of second messenger such as cyclic adenosine monophosphate (cAMP), Inositol, 1, 4, 5-triphosphate (IP3) and diacylglycerol (DAG). The second messengers activate ion channel including calcium channel inside the cell and sodium, potassium and calcium channel on extra cellular membrane. This ionization depolarizes the cell causing the release of neurotransmitters that send nerve impulses to the brain that carries the signal of bitter taste and taste blockers work by interfering with taste transduction(Fig. 4).

Effect of age on taste buds
Cells that make up the taste buds with age wear out, 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. Remaining taste buds becomes less sensitive. Researchers have been proved that that smoking and eating of scalding food may damage to taste buds. This lack 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 taste than any adults but because taste can be subjective. The mechanism that causes taste sensitivity in youngsters can be difficult to analyze.
Factors of infected taste buds:
Taste buds infection usually occurs due to vitamin B complex deficiency, long-term antibiotics drug therapy following radiation, smoking, vigorous rubbing by a rough tooth and thickening of tissues in elderly and fungal infection (oral thrush) in those with decreased immunity 9.

Ideal Properties of Taste Masking Process 10
An ideal taste masking process and formulation and characterization should have the following properties.

- 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
- Rapid and easy to prepare.

Factors Affecting Selection of Taste Masking Technology
Extent of Bitter Taste of the API
With aggressively bad tasting medicaments even a little exposure is sufficient to perceive the bad taste. For example, sweeteners could not achieve taste masking of oral formulation of ibuprofen due to its dominating taste 11. Coating is more efficient technology for aggressively bitter drugs even though coating imperfections, if present, reduce the efficiency of the technique 12. Similarly, microencapsulation of potent bitter active agents such as azithromycin is insufficient to provide taste masking of liquid oral suspensions 13. Viscosity enhancers can complement the taste masking efficiency. Oral suspension containing viscosity enhancers can masquerade the objectionable taste, which arises from the leakage of drug from the coated medicaments or microcapsules. This approach was also used for the microencapsulated oxazolidinone particles to limit the transport of drug from the polymer coated drug particles to the vehicle 14.

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 such as quinine, celecoxib, etoricoxib, antibiotics like levofloxacin, ofloxacin, sarpfoflaxin, ciprofloxacin, cefuroxime axetil, erythromycin and clarithromycin 15.

Dose of Active Pharmaceuticals
Dose of a drug may dictate whether a particular formulation strategy would be suitable to achieve taste masking. In pediatric formulations, the dose is small enough so as to allow the usage of flavoring agents to mask the taste of the medicine. For example, low dose palatable pediatric aspirin oral formulation was developed by adding sweeteners, but the same approach failed to address the problem of drugs like acetaminophen because of its high dose. In such cases, coating is preferred to achieve taste masking along with sweeteners to attain an acceptable final dosage form size 16.

Drug Particle Shape and Size Distribution
Particle characteristics of the drug would affect the taste masking process efficiency. Core materials with irregular shapes and small particle size lead to poor taste masking efficiency and varying dissolution of coated particles 17. Fines, abrasion and variable coating thickness can lead to situations wherein the taste mask coating is compromised. Multilayer coating using inner spacing layer to sequester the drug from taste masking layer helps to reduce or eliminate such coating imperfections. Taste masked granules of gatifloxacin and dextromethorphan were formulated by multilayer coating consisting of inner spacing layer followed by outer taste masking layer 11.

Dosage Forms
It is estimated that 50% of the population have problem of swallowing tablets, especially the pediatric and geriatric population. Chewable tablets and liquid oral dosage forms have been used to address these problems. However, it is difficult to formulate some drugs in these dosage forms due to their poor palatability 18. For formulations which are swallowed un chewed: capsules, coated tablets and slowly disintegrating hard tablets have been used as preferred taste masking technologies. Chewable tablets and liquid oral formulations are preferable in case of large dose drugs for an ease of intake. Taste masking technologies such as sweeteners, particulate coating, microencapsulation and granulation can be employed for chewable tablets and supported with techno-logies such as viscosity enhancers and pH modifiers to achieve taste masking in liquid oral formulations 19. Microencapsulation of the unpleasant tasting active agent with ethyl cellulose or a mixture of ethyl cellulose and hydroxypropyl cellulose or other cellulose derivatives has been used to provide chewable taste-masked dosage forms. However, this approach suffers from the disadvantage that the polymer coating releases the active agent in an inconsistent fashion and may not provide an immediate release. Moreover, coating is more suitable when the formulation is stored in a dry form. Viscosity enhancers or pH modifiers can be used in the suspending medium to achieve taste masking of suspended coated particles, especially for extremely bitter drugs like erythromycin and its derivatives during the shelf life of a reconstituted suspension 20.

Drug Solubility
Physicochemical properties of the drug play an important role in the selection of taste masking technology. For example, ondansetron has a relatively lower water solubility at higher pH, based on which a rapidly disintegrating taste masked composition of ondansetron was formulated by adding an alkalizing agent(sodium bicarbonate) to reduce the water solubility and the consequent taste perception 21. Douglas and Evans (1994) described different approaches to achieve the taste masking of ranitidine base and its salts having different solubility profiles. The bitter taste associated with a poorly soluble form of ranitidine may be satisfactorily masked by lipid coating of the drug substance. However, for water soluble forms of ranitidine (e.g. ranitidine hydrochloride), the degree of taste masking achieved by simple lipid coating of the drug substance may not be entirely satisfactory, particularly if the product is to be formulated in an aqueous medium. Thus ranitidine hydro-chloride was first incorporated into the inner core of a polymeric binder, or a lipid or wax having a melting point higher than that of the outer lipid coating to achieve an efficient taste masking 22.

Ionic Characteristics of the Drug
Ionic characteristics of drugs govern the selection of ion exchange resin polymers and the suitability of the drug candidate for this technology. For example, anionic polymers (e.g. alginic acid) are good candidates for cationic drugs like donepezil hydrochloride, and the cationic polymers are choice of excipients for anionic drugs like sildenafil 23, 24.
TASTE MASKING TECHNOLOGIES OF BITTER PHARMACEUTICALS

Taste masking technologies are very important for improving patient compliance and better therapeutic efficacy. Many oral drug delivery formulations have objectionable taste such as bitterness, saltiness or sourness. Taste masking technology includes two aspects:

- Selection of suitable taste masking substance such as polymers, sweeteners, flavors, amino acids etc.
- Selection of suitable taste masking techniques. A suitable taste masking technique can powerfully impact both, quality of taste masking and process effectiveness. There are many techniques developed for taste masking of bitter pharmaceuticals. These are as follows:

**Taste masking with sweeteners and flavors**

This technique 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.26, 27

**(A)Flavors**

**Natural Flavors**
- Juices - Raspberry
- Extracts - Liquorices
- Spirits - Lemon & Orange
- Syrups – Blackcurrant
- Tinctures -Ginger
- Aromatic waters - Anise & Cinnamon

**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) Sweeteners**
- Complement flavors associated with sweetness.
- Soothing effect on the membranes of the throat.

**Natural Sweetener:** Sucrose, glucose, fructose, Sorbitol, mannitol, glycerol, Honey, licorice.

**Artificial sweetener:** Saccharin, Saccharin sodium Aspartame.

**Nutritive:** Sucrose, Fructose and Glucose

**Polysols:** Mannitol, Sorbitol, Xylitol, Erythritol, Malitol.

**Non-Nutritive:** Aspartame, Sucralose, Neotame and Saccharine.

**Novel sweeteners:** Trehalose, Tagatose.

Table 1 presents a compilation of the most common artificial and natural sweeteners used in Pharmaceutical products, their relative sweetness and pertinent comments.

**Taste masking by Microencapsulation**

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**

One of the most important factor to be considered in taste masking by microencapsulation 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 ph6.8 but readily dissolve at gastric fluid ph1.2 could be a good candidate for taste masking. Before making a decision on coating material following factors must be considered:

- The particle size of the drug.
- Flow characteristics of the drug.
- Long term stability
- Moisture sensitivity
- Temperature of processing and most important
- Method delivery of active drug molecule.

**Table 2.** Presents the Taste masking of bitter drugs by microencapsulation.

**Taste masking by formulation of inclusion complexes**

In Inclusion complexes, host molecule has a cavity in which the guest drug occupies and the taste of the guest drug masked by two approaches40 as
- By decreasing its oral solubility on ingestion and
- By decreasing the amount of drug particles exposed to taste buds, reducing the perception of bitter taste.

Cyclodextrins are widely used in industry due to their ability to form inclusion complexes with a variety of molecules. Cyclodextrins are cyclic oligosaccharides composed of 6, 7, 8 glucose molecules (alpha-beta or gamma respectively) having supramolecular structures that involve intramolecular interactions41. Bitterness elimination is depend upon the extent of Complexation of guest molecule with host, value of complex association constant, temperature and the host / guest ratio (Fig 5 & 6).

For bitter drug forming a 1:1 complex with cyclodextrins, more than 99% of the bitter drug is complexed with cyclodextrins and as complexed molecule cannot react with the taste bud in the buccal cavity, no bitter taste perceived42 and suppression of bitter taste by
Cyclohexylcyclodextrin was increase in increasing order of alpha, gamma, and beta cyclodextrin. Taste masking by viscosity modification
Enhancement of viscosity in liquid formulations by thickening agents such as natural gums or carbohydrates can mask the unpleasant taste of drug by formulating a covering layer on the tongue and act as barrier between drug particles and taste buds, thus lowering the diffusion of drug from saliva into the taste buds. For viscosity enhancement in liquid formulations, polyethylene glycols and carboxy methylcellulose are induced which not only increases the stability of liquid formulation but surprisingly, provides taste masking of unpleasant tasting medicines. For examples, in cough syrups, terbutaline given in doses of 4mg/5ml can be effectively administered by increasing the viscosity of the formulation.

Taste masking by ion exchange resins (IER):
One of the popular approaches in the taste masking of bitter drugs is based on IER. IER are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium. Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert. The long-term safety of IER, even while ingesting large doses as in the use of cholestyramine to reduce cholesterol is an established unique advantage of IER due to the fixed positively or negatively charged functional groups attached to water insoluble polymer backbone. These groups have an affinity for oppositely charged counter ions, thus absorbing the ions into the polymer matrix. Since most drugs possess ionic sites in their molecule, the resin's charge provides a means to loosely bind such drugs and this complex prevents the drug release in the saliva, thus resulting in taste masking. For taste masking purpose weak cation exchange or weak anion exchange resins are used, depending on the nature of drug. The nature of the drug resin complex formed is such that the average pH of 6.7 and cation concentration of about 40meq/L in the saliva are not able to break the drug resin complex but is weak enough to break down by hydrochloric acid present in the stomach. Thus the drug resin complex is absolutely tasteless with no after taste, and at the same time, its bioavailability is not affected.

Classification of IER
IERs contain positively or negatively charged sites and are accordingly classified as either cation or anion exchanger. The functional group in cation exchanger and anion exchanger undergoes reaction with the cations and anions of the surrounding solution respectively. The strong cation exchanger contains sulphuric acid sites whereas weak cation exchangers are based on carboxylic acid moieties. The strong anion exchange resins have quaternary amine ionic sites attached to the matrix, whereas weak anion exchanger has predominantly tertiary amine substituents. Details of IERs are available which are summarized in Table 3.

Taste Masking by solid dispersion method
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. Various approaches for preparation of solid dispersion are described below:

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.

Taste Masking by Prodrug approach
Prodrugs are defined as therapeutic agents that are inactive moieties but on biotransformation liberate the pharmacologically active parent metabolites. By changing the molecular configuration of the parent molecule, the magnitude of a bitter taste response or taste receptor-substrate adsorption constant may be modified. Prodrugs can be used to increase or decrease the aqueous solubility, mask bitterness, increase lipophilicity, improve absorption, decrease local side effects, and alter membrane permeability of the parent molecule.

Tasteless/bitterless prodrugs of opioid analgesics and antagonists were formulated for improved buccal delivery, when administered as prodrugs; the bioavailability was improved without visible adverse effects. Table 4 shows Prodrug with improve taste masking.

Taste masking by Adsorption
Adsorbates are commonly used with other taste masking technologies. The drug may be adsorbed or/and entrapped in the matrix of the porous component, which may result in a delayed release of the bitter active during the transit through the oral cavity thereby achieving taste masking. Kashid et al. (2007) developed a taste masked loperamide formulation with magnesium aluminium silicate by blending the drug and the adsorbate, and further granulating with hydrophobic polymers to achieve taste masking.

Taste masking by pH modifiers
pH Modifying agents are capable of generating a specific pH microenvironment in aqueous media that can facilitate in situ precipitation of the bitter drug substance in saliva thereby reducing the overall taste sensation for liquid dosage forms like suspension. Wyley (2004) described an appli-cation of pH modifying agent such as L-arginine for taste masking of bitter medicament. L-arginine maintains alkaline pH of the suspending vehicle to promote in situ precipitation of desquinolone in saliva. Redondo and Abanades (2003) developed taste masked liquid formulation of ibuprofen by using sodium saccharin and pH regulating agents.

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 amiprolone 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.

Taste masking by multiple emulsion technique
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.69

**Taste masking by 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. Sodium salts such as Sodium chloride, Sodium acetate and Sodiumglucoconate have been shown to be potent inhibitors of some bitter compounds. The mechanism is not known, however, research shows that sodium act at peripheral taste level rather than a cognitive effect.60,61

**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.62

**Desensitizing agents**
Desensitizing agents like phenols, sodium phenolates desensitize the taste buds by interfering with taste transduction (Fig. 4), the process by which taste message from the mouth to the brain and thus mask the taste of drug.60

**Molecular complexes of drug with other chemicals**
Molecular complexes can minimize the intensity of bitterness by modifying the solubility and absorption of drug by the formation of complex. This usually decreases the intensity of bitterness of drugs. Higuchi and Pitman reported that caffeine forms complexes with organic acids that are less soluble than xanthenes sand as such can be used to decrease the bitter taste of caffeine.62

**Use of amino acids**
Amino acids and their salts (alanine, taurine, glutamic acid, glycine) in combination with bitter drugs reduces the bitterness of the drugs for example, 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.62

**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 alky Carbonates of Clarithromycin have remarkably viated bitterness and improved bioavailability when administered.64

**Taste Masking with Lipophilic Vehicles like lipids and lecithins**
Oils, surfactants, polyalcohols, and lipids effectively increase the viscosity in the mouth and coat the taste buds, and therefore they are potential taste masking agents.65,66 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 in pharmaceuticals. Magnesium aluminum silicate with soybean lecithin is used to mask the unpleasant taste of talamicillin HCl.66

**Development of Liposome**
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-hydroxyethylpiperazine-N’- 2- ethane sulfonic acid) buffer at pH 7.2.67

**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 could be masked. Granulation lowers the effective surface area of the bitter substance that come 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, e.g., rapidly disintegrating tablet and chewable tablet. Taste masked granules of bitter tasting drug Pirenzepine and Oxybutynin have been prepared by the extrusion using Aminoalkylmethacrylate copolymer.68,69

**Miscellaneous taste masking approaches**
(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 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.

(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.

(C) Continuous multipurpose melt (CMT) technology68

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.

EVALUATION TECHNIQUES

Sensory evaluation

Taste 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)74

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 Responses75

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

(c) Electronic (E) tongue76

This is an automated taste sensing device (Fig. 7) 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. 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. Secondly, for anionic drugs, such as Diclofenac sodium or Salicylic acid, the positively charged membrane in channel 5 or 6 seemed to the useful even though they are being sour rather than bitter. For drugs with both an Amino (cationic) groups 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 component will be needed for a complete evaluation of the bitterness of medicines.

(d) Spectrophotometric Method78

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.

CONCLUSION

Taste masking is a viable strategy to improve the patient compliance, especially for bitter drugs, whereby, a gamut of methodologies may be adopted to deliver a palatable formulation. Taste masked products developed from innovative pharmaceutical technologies not only increase the commercial profits, but also create brand value for a company. Use of sweeteners is an age old and most popular tool for disguising bitterness, the present trend has been towards exploring intense sweeteners of natural origin that can hasten commercialization. Also, the combination of sweeteners with other taste masking technologies including microencapsulation, particulate coating, bitterness blockers, ion exchange resins and prodrug formation are found to be a more efficient strategy. Improvement in coating technology by use of multiple or spacer layers and a shift to aqueous based coating of hydrophobic polymers are the newer trends. However, the technique requires specialized skills for optimization and scale up of the process. Granulation, a simpler technology finds more use of swelling polymers for efficient taste masking. Amongst the strategies employed, bitter taste blockers/inhibitors which specifically block the bitter taste but not the pleasant taste of any additive are being explored as universal taste masking alternatives. With ongoing advancements, using a combination of various taste masking technologies, future looks promising for taste masking of bitter drugs.

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REFERENCES

1. Patel A, Anjir S. Formulation Taste Masking-From Bitter to better: The latest taste masking techniques can yield more palatable drugs. Pharm Formulation and Quality 2012:1-3.69
6. Siegel SA. Swallowing the bitter pill: Old and new approaches to taste masking Formulating better medicines for children. Royal pharmaceutical society 2009; 1-35.74


Wiley GJ: MXPAA08720. 2004


Mundada AS, Chachda NO, Jasmine G. Taste masking approaches – A Review part-II. Amer Pharm Review. 1-3.


Wiley GJ: MXPAA08720. 2004


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Fig. 1 Physiology of Taste Bud

Fig. 2 Taste Points in Tongue

Fig. 3 Taste Signaling Pathways

Fig. 4 Taste Blocking Mechanism

Fig. 5: Cyclodextrin Drug complex in 1:1 ratio

Fig. 6: Cyclodextrin Drug complex in 1:2 ratios
Table 1: Relative sweetness of commonly used sweeteners

<table>
<thead>
<tr>
<th>Sweetener</th>
<th>Relative Sweetness</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspartame</td>
<td>200</td>
<td>Not very stable in solution</td>
</tr>
<tr>
<td>Acesulfame potassium</td>
<td>137-200</td>
<td>Bitter after taste if used in higher concentration</td>
</tr>
<tr>
<td>Cyclamate</td>
<td>40</td>
<td>Banned</td>
</tr>
<tr>
<td>Glycerin</td>
<td>50</td>
<td>Moderately Expensive</td>
</tr>
<tr>
<td>Lactose</td>
<td>0.16</td>
<td>Large amount required</td>
</tr>
<tr>
<td>Mannitol</td>
<td>0.60</td>
<td>Negative heat of solution</td>
</tr>
<tr>
<td>Saccharine</td>
<td>450</td>
<td>Unpleasant after taste</td>
</tr>
<tr>
<td>Sucrose</td>
<td>1</td>
<td>Most commonly used</td>
</tr>
<tr>
<td>Sucralose</td>
<td>600</td>
<td>Synergizing sweetening effect</td>
</tr>
</tbody>
</table>

Table 2: Taste masking by Microencapsulation

<table>
<thead>
<tr>
<th>Technique</th>
<th>Polymer</th>
<th>Taste Masked Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air Suspension Coating</td>
<td>Methacrylic acid copolymer</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Phase separation Coacervation</td>
<td>Eudragit E-100, Chitosan</td>
<td>Clarithromycin, Paracetamol</td>
</tr>
<tr>
<td>Fluidized Bed / Spray Coating</td>
<td>Hydrogenated Oil and Surfactant</td>
<td>Indeloxazine</td>
</tr>
<tr>
<td>Solvent Evaporation Method</td>
<td>Eudragit E, PEG, Ethyl Cellulose</td>
<td>Pseudoephedrine, Ramitidine</td>
</tr>
<tr>
<td>Extrusion Coating</td>
<td>Eudragit E-100</td>
<td>Oxybutinin, Ofloxacin, Pirezepin</td>
</tr>
</tbody>
</table>

Table 3: Examples of IER – drug complex

<table>
<thead>
<tr>
<th>Name</th>
<th>Functionality</th>
<th>Polymer backbone</th>
<th>Medicament</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amberlite IRP64</td>
<td>Weak acid COO-</td>
<td>Crosslinked polyacrylic</td>
<td>Dextromethorphan, Dimenhydrinate</td>
</tr>
<tr>
<td>Amberlite IRP69</td>
<td>Strong acid SO3-</td>
<td>Styrene-Divinyl Benzene</td>
<td>Ranitidine</td>
</tr>
<tr>
<td>Amberlite IRP88</td>
<td>Weak acid COO-</td>
<td>Crosslinked polyacrylic</td>
<td>Talampacillin-HCl, Paroxetine</td>
</tr>
<tr>
<td>Indion 204</td>
<td>Weak acid COO-</td>
<td>Crosslinked polyacrylic</td>
<td>Norfloxacin, Ofloxacin</td>
</tr>
<tr>
<td>Indion 214</td>
<td>Weak acid COO-</td>
<td>Crosslinked polyacrylic</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>Indion 234</td>
<td>Weak acid COO-</td>
<td>Crosslinked polyacrylic</td>
<td>Ciprofloxacin, Chloroquin phosphate</td>
</tr>
<tr>
<td>Kyron T-104</td>
<td>Weak acid COO-</td>
<td>Crosslinked polyacrylic</td>
<td>Cefpodoxime proxetil</td>
</tr>
<tr>
<td>Kyron T-114</td>
<td>Weak acid COO-</td>
<td>Crosslinked polyacrylic</td>
<td>Ofloxacin</td>
</tr>
<tr>
<td>Kyron T-134</td>
<td>Weak acid COO-</td>
<td>Crosslinked polyacrylic</td>
<td>Metronidazole</td>
</tr>
</tbody>
</table>

Table 4: Prodrug with improved taste masking

<table>
<thead>
<tr>
<th>Parent Drug</th>
<th>Prodrug with improved taste</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>Alkyl ester</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Palmitate or phosphate ester</td>
</tr>
<tr>
<td>Trimcinolone</td>
<td>Diacetate ester</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Alkyl ester</td>
</tr>
<tr>
<td>Lincomycin</td>
<td>Phosphate or alkyl ester</td>
</tr>
<tr>
<td>Tetracyclin</td>
<td>3,4,5-Trimethoxy benzoate salts</td>
</tr>
</tbody>
</table>