REVIEW ON: TASTE MASKING APPROACHES AND EVALUATION OF TASTE MASKING

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ABSTRACT

Oral administration of pharmaceuticals is one of the most popular method of drug dilevery. Many orally administered drugs elicit bitter taste. Taste masking becomes a prerequisite for bitter drugs to improve the patient compliance especially in the pediatric and geriatric population. Formulating orodispersible, melt in mouth, buccal tablet and other formulations which comes in contact with taste buds taste is one of critical factor to be consider. Masking the bitter taste of drugs is a potential tool for the improvement of patient compliance which intern decides the commercial success of the product. This paper reviews different methods are available to mask undesirable taste of the drugs, with the applications. It includes adding sugars, flavors, sweeteners, use of aminoacids, coating drug, multiple emulsion, viscosity modifier, vesicles and liposomes, prodrug and salt formation, inclusion and molecular complexes, solid dispersion, application of Ion Exchange Resins (IERs).

KEYWORDS: Taste masking, Flavours, Cyclodextrins, E-tongue, IER.

INTRODUCTION:

Children, older persons, and many other persons including disabled or incapacitated patients often have trouble swallowing tablets or capsules. In these situations, it is desirable to provide the drug either in a chewable solid form or a liquid dosage form. [14] The 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. [3] Masking of bitter taste of drugs is an important parameter for the improvement of patient compliance. [1] The problem of bitter and obnoxious taste of drug in pediatric and geriatric formulations is a challenge to the pharmacist in the present scenario. [4]

Chemoreceptors on the Tongue

Taste is the brain's interpretation of chemicals that trigger receptors on the tongue, which are housed in the taste buds. Molecule interacts with taste receptor on the tongue to give taste sensation, when they dissolve in saliva. This sensation is the result of signal transudation from the receptor organs for taste, commonly known as taste buds. These taste buds contain very sensitive nerve endings, which produce and transmit electrical impulses via the seventh, ninth and tenth cranial nerves to those areas of the brain, which are devoted to the perception of taste. [4,5]

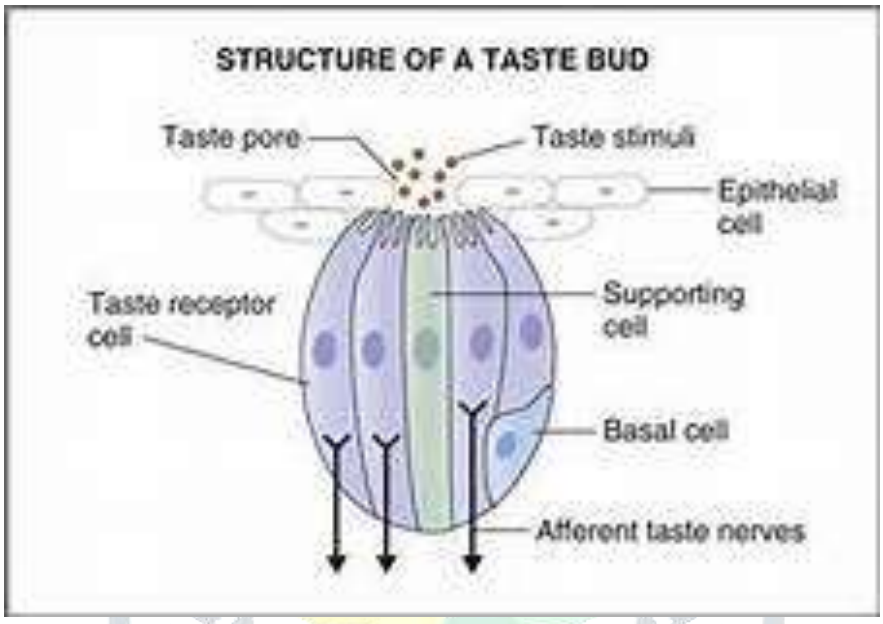

Fig.1 Physiology of Taste Bud

Four fundamental sensations of taste have been described: Sweet and salty, mainly at the tip. Sour, at the sides. Bitter, at the back. [5] and fifth widely accepted basic taste is Umami. [1]

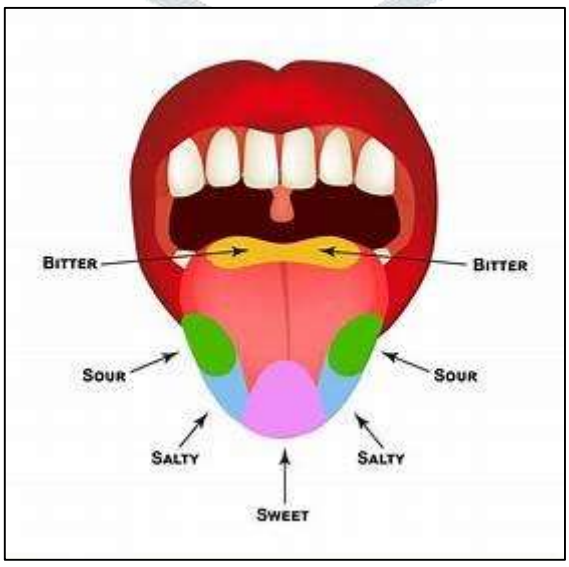

Fig. 2 Taste Points in Tongue

Taste Signaling Pathways

Taste transduction begins with the interaction of a tastant (eg. medicine or food) with taste receptor cells in the taste buds (Fig 3). The tastant binds with G- Protein coupled receptors (GPCRS) in the cells triggering the release the release of G-Protein called Gustducin. [1]

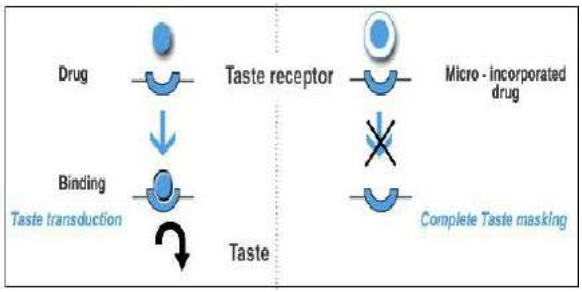

Fig. 3 Taste Signaling Pathways

Taste Blocking Mechanism

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 calcium ion channel inside the cell and sodium, potassium and calcium channel on extra cellular membrane. Ionization depolarizes the cell causing 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. [9]

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TASTE MASKING TECHNOLOGIES:

Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist. [14] Methods commonly used for taste masking involves various physical and chemical method that prevent the interaction of taste bud with drugs, Two approaches are commonly utilized to overcome bad taste of the drug.

1. By reducing the solubility of drug in the pH of saliva (5.6 - 6.8).
2. By altering the affinity and nature of drug which will interact with the taste receptor. [7]

An ideal taste masking process and formulation should have the following properties.

- Involve least number of equipments and processing steps.
- Effectively mask taste with as few excipients which are economically and easily available.
- No adverse effect on drug bioavailability.
- Least manufacturing cost.
- Can be carried out at room temperature.

- Require excipients that have high margin of safety
- Rapid and easy to prepare. [2,3,12]

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

1) Extent of the bitter taste of the API.

2) Required dose load.

3) Drug particulate shape and size distribution.

4) Drug solubility and ionic characteristics.

5) Required disintegration and dissolution rate of the finished product.

6) Desired bioavailability.

7) Desired release profile.

8) Required dosage form. [3]

Factors affecting selection of taste masking technology

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, Sweeteners could not achieve taste masking of oral formulation of ibuprofen due to its dominating taste. Coating is more efficient technology for aggressively bitter drugs even though coating imperfections, if present, reduce the efficiency of the technique. Similarly, microencapsulation of potent bitter active agents such as azithromycin is insufficient to provide taste masking of liquid oral suspensions. [11]

Taste Masking Technologies

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

1. Taste masking with flavors, sweeteners & amino acids
2. Polymer coating of drug
3. Formation of inclusion complexes
4. Ion exchange resin complexes
5. Solid dispersion
6. Microencapsulation
7. Multiple Emulsions
8. Development of Liposome
9. Prodrug approach
10. Taste masking by adsorption
11. Taste Masking with Lipophilic Vehicles like lipids and lecithins
12. Taste Suppressants and Potentiators
13. Taste masking by gelation
14. Formation of salt and derivative
15. Use of Amino Acids and Protein Hydrolysates

16. Miscellaneous.

a) By effervescent agents

b) Rheological modification

c) Continuous multipurpose melt (CMT) technology

d) Wet Spherical Agglomeration (WSA) [2,6]

1 . Taste masking with Flavors, Sweeteners and amino acids :

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

Flavors

Basis of Choosing a Flavor

1. Complementary to existing flavor of the drug

2. Known popularity of particular flavors

3. Age of patients

4. Allergy

Natural Vs Synthetic

1. Cheaper

2. More readily available

3. Less variable in chemical composition

4. More stable Flavoring agents for taste masking [4]

Natural Flavors- Raspberry Juices; Liquorices Extract; Lemon & Orange Spirits; Blackcurrant Syrups; Ginger Tinctures; Anise & Cinnamon Aromatic waters; Peppermint & Lemon Aromatic Oils.

Synthetic Flavors- Alcoholic solutions; Aqueous solutions; powders. [10]

Sweeteners

- Complement flavors associated with sweetness
- Soothing effect on the membranes of the throat [2]

Natural Sweetener- Sucrose, Glucose, Fructose, Sorbitol, Mannitol, Honey, Glycerol, Liquorice.

Artificial Sweetener- Saccharin, Saccharin Sodium, Aspartame. Nutritive Sweeteners- Sucrose, Fructose, Glucose. Non-Nutritive Sweeteners- Aspartame, Sucralose, Neotame, Saccharine. Polyols- Mannitol, Sorbitol, Xylitol, Erythritol, Maltitol. Novel Sweeteners- Trehalose, Tagatose. [3]

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Novel Sweeteners- Trehalose, Tagatose. [3] Table 1. List of FDA approved Non-Nutritive Sweeteners [3,14]

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 . [1]

2. Polymer coating of drug

This is the simplest and most feasible option to achieve taste masking. The coating acts as a physical barrier to the drug particles, thereby minimizing interaction between the drug and taste buds. Coating of chewable tablets provides excellent taste masking while still providing acceptable bioavailability. [14] In this approach, powders as fine as 50 mm 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. [9] Any nontoxic polymer that is insoluble at pH 7.4 and soluble at acidic pH, would be an acceptable alternative for taste masking. Taste masking of ibuprofen has been successfully achieved by using the air suspension coating technique to form microcapsules, which comprises a pharmaceutical core of a crystalline ibuprofen and methacrylic acid copolymer coating that provides chewable taste masked characteristics. [2]

Agents used for coating

- Carbohydrates (Cellulose)
- Synthetic polymers (Eudragits etc)
- Proteins, Gelatine, and Prolamines (Zein)
- Zeolites [14]

It is classified based on the type of coating material, coating solvent system, and the number of coating layers. Hydrophobic polymers, lipids, sweeteners and hydrophilic polymers can be used as coating materials, either alone or in combination. [10] Multilayer coating has been used to overcome the challenges of coating imperfections, which otherwise lead to a decline in the taste masking performance, especially for the aggressively bitter drugs. The core materials were coated with a first smooth and uniform spacing layer, which can minimize the coating imperfections during the second layer coating and can also act as an instant barrier between the taste receptors and the bitter core material. [10]

3. Formation of inclusion complexes

In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent, i.e. the host molecule, forming a stable complex, a low stability constant would lead to a rapid release of free drug in the

oral cavity, resulting in inefficient taste masking. [9,15] 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. [1] Vander Walls forces are mainly involved in inclusion complexes. The complexing agent mask the bitter taste of drug by either decreasing its oral solubility or decreasing the amount of drug particles exposed to taste buds, thereby reducing the perception of bitter taste. This method is most suitable only for low dose drugs. ,-CD is the most widely used complexing agent for inclusion type complexes. It is a sweet, non-toxic, cyclic oligosaccharide obtained from starch. [4] Hydrophobic drugs form complex by replacing ëinclusion waterí while easily migrating (hydrophilic, well soluble) drugs form complex, assuming replacement of ëcrystal waterí. Physical Mixture (PM), Kneading Method (KM), Solid dispersion/co-evaporated dispersion method, Precipitation method. [15]

4. Ion exchange resin complexes

Ion-exchange resins (IERs) are high molecular weight polymers with cationic and anionic functional groups attached to water insoluble polymer backbone. These groups have an ability to exchange [16] 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 weak ionic bonding so that dissociation of the drug-resin complex does not occur under the salivary pH conditions, 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. [11]

5. 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 melting (fusion) solvent or melting solvent method. [3] Solid dispersion of drug with the help of polymers, sugar, or other suitable agents, is very useful for taste masking. [14] Carriers used in solid dispersion systems include povidone polyethylene glycols, hydroxypropyl methylcellulose, urea, mannitol and ethylcellulose. Various approaches for preparation of solid dispersion are described below. [4,9]

Melting method

In this method, the drug or drug mixture and a carrier are melted together by heating. The melted mixture is cooled & solidified rapidly in an ice bath with vigorous stirring. The final solid mass is crushed & 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. iii) Melting solvent method In this method drug in solutions is incorporated into molten mass of polyethylene glycol at a temperature 70˚C without removing

the solvent. The bitter taste of dimenhydrinate can be masked by preparing the solid dispersion of the drug with polyvinyl acetate phthalate.

6. Microencapsulation

Microencapsulation is a process of applying relatively thin coating to small particles of solids, droplets of liquids and dispersions, using various coating agents, such as gelatin, povidone, hydroxyethyl cellulose, ethyl cellulose, bees wax, carnauba wax acrylics and shellac. [4,5,9] 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. [3] Polymers have been exclusively used as coating materials, either alone or in combination, as a single or multi-layer coat, in the taste masking of bitter medicaments. Combinations of pH independent water insoluble polymers such as cellulose ethers, cellulose ester, polyvinyl acetate and water soluble polymers such as cellulose acetate butyrate, Polyvinylpyrrolidone, hydroxyethyl cellulose have been used to attain a balance between the taste masking and in vitro release. The unpleasant taste of clarithromycin was masked when the drug was encapsulated in combination of d acrylic resins such as Eudragit L-100, Eudragit S-100 .

7. Multiple Emulsions

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. If the system is stable enough for a reasonable shelf life, the formulation could also mask the taste of drug. 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. [6]

8 . Miscellaneous.

By 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 was formulated to supply the medicament 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 non active material, such as sweeteners, flavouring components, and fillers. [14] 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. [3]

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. [4] 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 agents such as polyethylene glycol and sodium carboxy methylcellulose. [6,9] Acetaminophen suspension can be formulated with xanthan gum (0.1-0.2%) and microcrystalline cellulose (0.6-1%) to reduce bitter taste. [14] The antidepressant drug mirtazapine is formulated as an aqueous suspension using methonine (stabilizer) and maltitol (thickening agent). Maltitol is stable in the acidic pH range of 2 to 3 and besides masking the unpleasant taste of the drug, it also inhibit its undesirable local anesthetic effect. [3] cough syrups, terbutaline given in doses of 4mg/5ml can be effectively administered by increasing the viscosity of the formulation. [1]

Continuous multipurpose melt (CMT) technology

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. [3,14]

Wet Spherical Agglomeration (WSA)

A novel Microencapsulation process combined with the wet spherical agglomeration (WSA) technique was used to mask the bitter taste of enoxacin. [14]

EVALUATION

Sensory evaluation Taste, to think of, is a very subjective perception. Depending on individuals, the perceived taste may vary to different degrees. To quantitatively evaluate taste sensation, following methods have been reported in literature. 1. Panel testing (human subjects) 2. Measurement of frog taste nerve responses. 3. Multichannel taste sensor/ magic tongue 4. Spectrophotometric evaluation/ D30ís value [2] A. In vivo Evaluation

1. **Panel testing (human subjects)**

   The panel testing is a psychophysical rating of the gustatory stimuli. In vivo taste evaluation carried out on a trained taste panel of 5-10 healthy volunteers with organoleptic sense, with their prior consent. On placing the dosage form in mouth for 60 seconds, bitterness recorded against pure drug using a numerical scale. The numerical scale may bears values as 0 = pleasant, 1 = Tasteless, 2 = No bitter but after taste give bitterness, 3= immediately gives bitterness, 4 = slightly bitter, 5 = extremely bitter. In vivo assessment usually demands large panels and elaborate analysis, raises safety and scheduling issues and can be time consuming and expensive. [1,2]

2. 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 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.[2,3]

B. In vitro Evaluation

1. Multichannel Taste Sensor / Magic tongue

Invention of ìE-Tongueî electronic sensor array technology overcomes this problem, which is a device for recognition, quantitative multicomponent analysis and artificial assessment of taste and flavor. It recognizes three levels of biological taste including receptor level (Taste buds in humans, probe membranes in E-Tongue), circuit level (neural transmission in humans, transducer in E-Tongue), and perceptual level (cognition in the thalamus humans, computer and statistical analysis in the E-Tongue). The probes consist of a silicon transistor with proprietary organic coatings, which govern the probeís sensitivity and selectivity, and measurement done potentiometrically. Each probe is cross selective to allow coverage of full taste profile and statistical software interprets the sensor data into taste patterns. Liquid samples directly analyzed without any preparation, whereas solids require a preliminary dissolution before measurement. Reference electrode and sensors are dipped in a beaker containing a test solution for 120 seconds (fig. 8). A potentiometric difference between each sensor and a reference electrode measured and analyzed by the E-Tongue software. [1] Quinine hydrochloride was taken as the standard for bitterness. [3] 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. [6]

These data represent the input for mathematical treatment that will deliver results. The E-Tongue enables us to test taste accurately without the need for human volunteers at earlier stages of drug development. Furthermore, the E-Tongue cannot be poisoned and it wonít fatigue or lose its sense of taste after long periods of testing. The bitterness of drugs and their compatibility with taste masking agents that does not affect the bioavailability of drug.[1] 2. 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 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 100Ïg/ml. [2,3] Generally the taste evaluation involves the objective or analytical method and subjective or hedonic method. [6]

CONCLUSION:

Taste masking of bitter drugs has been a challenge to the scientist. We have made an attempt to describe various methods, which could be suitable for taste masking of bitter drugs. There are number 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. The methods described in this review can be used for bench scale as well as pilot scale also.

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