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TASTE MASKING- A REVIEW ON IMPROVEMENT OF PATIENT COMPLIANCE FOR PAEDIATRICS AND GERIATRICS

Prathamesh A Shinde*, Shivram N Jondhale, Arjun K Jadhav

NDMVP'S College of Pharmacy, Gangapur Road, Nashik-422002, Maharashtra, India.

Keywords:

Taste, taste buds, taste masking technologies, evaluation of taste masking, electronic tongue, challenges in developing formulation for paediatrics

For Correspondence:

Prathamesh A Shinde

NDMVP'S College of Pharmacy, Gangapur Road, Nashik-422002, Maharashtra, India

E-mail:

shindeprathamesh321@gmail.com

ABSTRACT

Most active pharmaceutical ingredients (APIs) are highly bitter and this is the main difficulty behind the palatable preparation for paediatric therapy. Adult formulations can be easily taste masked by coating the tablet or by putting the drug in capsule dosage form. Palatability of paediatric formulation is of greater importance when it comes to bitter active ingredients. So many advancements have taken place in the field of taste masking. Along with this the need to achieve global regulatory acceptability of such formulation is on rise. This creates a situation where more children are in safe and effective medications. Main objective of this review article is to give a view on various taste masking technologies employed in pharmaceutical field and challenges for developing paediatric formulations. The review also covers various taste assessment methods including Human volunteer method and application of Electronic tongue in pharmaceutical field.

1. INTRODUCTION

Taste is one of the most important parameters governing patient compliance. Undesirable taste is one of several important formulation problems that are encountered with certain drugs. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially pediatric patients. Several oral pharmaceuticals, numerous food and beverage products and bulking agents have unpleasant, bitter-tasting components. So any pharmaceutical formulation with a pleasing taste would definitely be preferred over a product and would translate into better compliance and therapeutic value for the patient and more business and profits for the company. The desire of improved palatability in these products has prompted the development of numerous formulations with improved performance and acceptability.[1] Organoleptic characteristics of pharmaceutical products i.e. taste, odor and appearance are essential factors in assessing the patient's acceptability; out of these organoleptic characteristics taste is an important parameter governing patient compliance.[2] Taste masking in the present day pharmaceutical industry has become a potential tool to improve patient compliance and commercial success of the product.[3] "Worst the taste of the medication, the better the cure" was once the prevailing attitude. Today this trend has changed and great importance is given to the organoleptic characteristics of pharmaceutical products. Masking of the unpleasant taste of a drug improves the compliance of the patient and product value.[4] Unwillingness to swallow solid dosage form such as tablets is a general problem for all age groups, especially elderly and pediatrics mainly due to the physiological changes. Forty five per cent of stroke survivors, thirty three per cent of nursing home residents and sixty three per cent of cancer patients undergoing palliative care in the community or hospital report dysphagia.[5]

2. Taste:

Taste is a survival mechanism, alerting us to potentially harmful or potentially nutritious substances. We process taste at three levels: the receptor level, the circuit level, and the perceptual level. At the receptor level are approximately 10,000 chemoreceptors or taste buds, residing primarily on the tongue, with some delocalized receptors at the back of the throat. These receptors fall into five primary categories: bitter, sour, umani, salt, and sweet, with grouped receptors dissipated over the surface of the tongue for each stimulus. Sweet signals carbohydrates or certain amino acids. Sour characterizes vitamins. Salt detects needed minerals. Umani indicates protein and amino acids. In general, we experience these tastes as

pleasant. Bitter sensation, however, is often unpleasant, suggesting alkaline water, alkaloid poisons, and spoiled foods. APIs, of course, usually fit into the bitter category.[6]

Anatomy and Physiology of Taste Buds:

In mammals taste buds are aggregation of 30-100 individual elongated "neuroepithelial" cells, which are often embedded in specialization of surrounding epithelium, termed papillae (Fig. 1.1A & 1.1B). At the apex of the taste bud, microvillar processes protrude through a small opening, the taste pore, into the oral milieu (Fig.1.1C). At the base of the taste bud, afferent taste nerves invade the bud and ramify extensively, each fiber typically synapsing with multiple receptor cells within the taste bud.

Location of taste buds[7]:

The taste buds are found on different types of papillae on the tongue:

1. A large number of taste buds are on the wall of the troughs that surrounds the circumvallated papillae, which forms 'v' line on the posterior surface of the tongue.
2. Moderate numbers of taste buds are on fungi form papillae over the flat anterior surface of the tongue.
3. Moderate numbers are on the foliate papillae located in the folds along the lateral surface of the tongue.
4. Additional taste buds are located on the palate and few on the tonsillar pillars, the epiglottis and even in the proximal esophagus.
5. Innervations of tongue: The receptor cell does not have axons. Transmitter relays information onto terminals of sensory fibers. These fibers arise from the ganglion cells of the cranial nerves VII (facial - branch called the chorda tympani) and IX (glossopharyngeal)

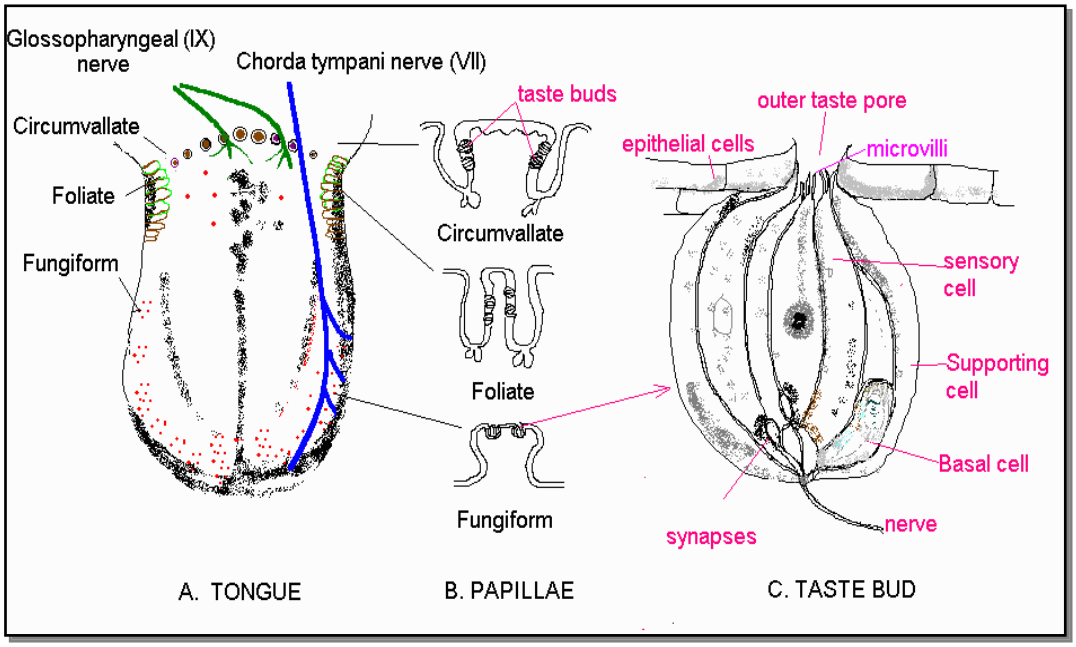

Figure 1.1: Papillae and taste buds[6]

3. Mechanism of Stimulation of Taste[8]:

The membrane of the taste cell, like that of other sensory receptor cells, is negatively charged on the side with respect to outside. Application of taste substance to the taste buds causes partial loss of this negative potential- i.e. cell is depolarized. The decrease in potential,within the wide range,is approximately proportional to logarithm of concentration of stimulating substance. This change in the potential in the taste cell is the receptor potential for taste. The mechanism by which most stimulating substance react with the taste villi is by binding of the taste chemicals to the protein receptor molecule that protrude through the villus membrane. This in turn allows sodium to enter and depolarize the cell. Then the taste chemical is gradually washed away from the taste villus by saliva, which removes the stimulus.

1) Salt taste: Na^+ ions enter the receptor cells via Na-channels. These are amilorid-sensative Na^+ channels .The entry of Na^+causes a depolarization, Ca^+ enters through voltage sensitive Ca^+ channels, transmitter release occurs and results in increased firing in the primary afferent nerve.

2) Sour taste: Sour taste is acidic. H^+ ions block K^+ channels and are responsible for maintaining the cell membrane potential at hyperpolarized level. Block of these channels causes a depolarization; Ca^+ entry causes transmitter release and increased firing in the primary afferent nerve.

3) Sweet taste: There are receptors in the apical membrane that bind glucose (sucrose - a combination of glucose and fructose - and other carbohydrates). Binding to the receptor activates adenyl cyclase, thereby elevating cAMP. This causes a PKA-mediated phosphorylation of K^+ channels, inhibiting them. Depolarization occurs Ca^{2+} enters the cell through depolarization-activated Ca^{2+} channels; transmitter is released increasing firing in the primary afferent nerve.

4) Bitter taste: Bitter substances causes the second messenger (IP_3) mediated release of Ca^{2+} from internal stores (external Ca^{2+} is not required). The elevated Ca^{2+} causes transmitter release and this increases the firing of the primary afferent nerve.

5) Umani taste: Umani is the taste of certain amino acids (e.g. glutamate, aspartate and related compounds). Recently it has been shown that the metabotropic glutamate receptor (mGluR4) mediates umani taste. Binding to the receptor activates a G-protein and this may elevate intracellular Ca^{2+}. Monosodium glutamate, added to many foods to enhance their taste (and the main ingredient of soy sauce), may stimulate the umani receptors. But, in addition,

there are ionotropic glutamate receptors (linked to ion channels), i.e. the NMDA-receptor, on the tongue. When activated by these umani compounds or soy sauce, non-selective cation channels open, thereby depolarizing the cell. Calcium enters, causing transmitter release and increased firing in the primary afferent nerve[6].

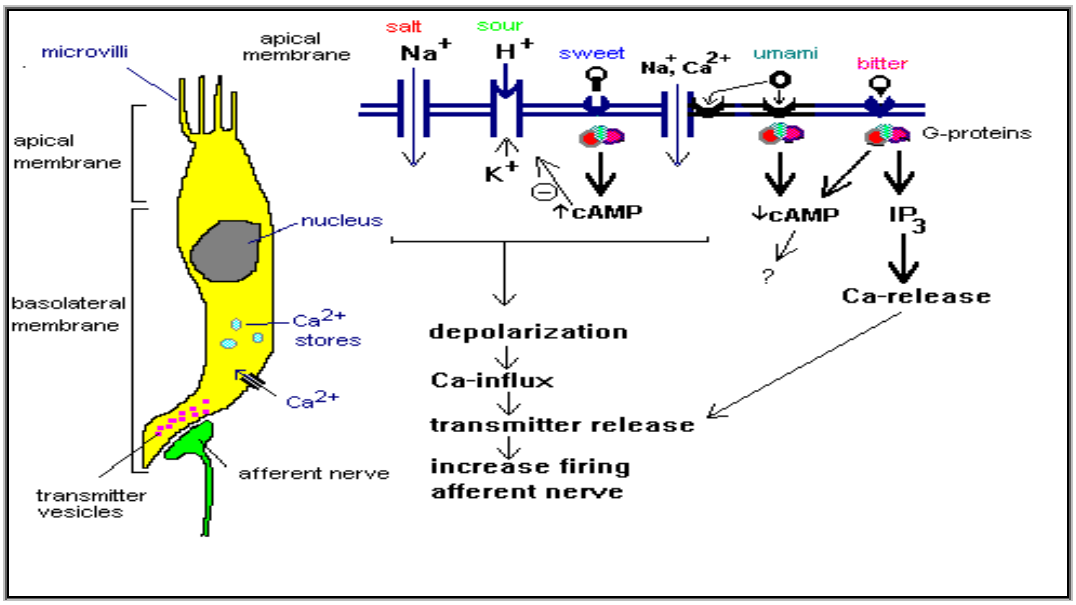

Figure 1.2: Mechanism of taste perception[6]

Ideal properties of taste masking process [9]:

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 bioavailability.
- Require excipents that are economical and easily available.
- Least manufacturing cost.
- Can be carried out at room temperature.
- Excipients are of high safety.
- Rapid and easy to prepare.

4. **Factors affecting selection of taste masking technology:**

A. Extent of Bitter Taste

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. [10] Coating is more efficient technology for aggressively

bitter drugs even though coating imperfections, if present, reduce the efficiency of the technique.[11] Similarly, microencapsulation of potent bitter active agents such as azithromycin is insufficient to provide taste masking of liquid oral suspensions.[12] 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.[13]

B. 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.[14]

C. 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.[15] 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.[10]

D. 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.[16] For formulations which are swallowed unchewed: 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 technologies such as viscosity enhancers and pH modifiers to achieve taste masking in liquid oral formulations.[17] 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.[18]

E. 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.[19] 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 hydrochloride 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.[20]

F. 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.[21, 22]

5. Taste masking technologies for Bitter actives:

Using suitable agents one can reduce the unpleasant taste of bitter actives. But universally acceptable taste-masking technology does not seem to exist. Many current taste masking efforts are directed at reducing the negative attributes of paediatric dosage forms, which is a big challenge. Finding a suitable taste masking method can impact the quality of taste masking and process effectiveness. There are many techniques developed for taste masking of bitter actives. These are as follows.

5.1 Sensory approaches

- **a.** Flavoring agents, sweeteners and amino acids
- **b.** Numbing taste buds

5.2 Chemical approaches

- **a.** Prodrugs
- **b.** Salt preparation

5.3 Barrier approaches

- **a.** Viscosity modifier
- **b.** Coating by wet granulation
- **c.** Emulsions
- **d.** Liposomes
- **e.** Microspheres/Microcapsules

5.4 Complexation and adsorption

- **a.** Adsorbate formation
- **b.** Inclusion complexation
- **c.** Complexation with ion exchange resins/polymers

6.1 Sensory approach.

a. Flavoring agents, Sweeteners and Amino Acid. [23, 24, 25, 26, 27]

It is important to understand that only soluble portion of the drug can generate the sensation of taste. Addition of flavors and sweeteners is the foremost and simplest approach for taste masking especially in case of pediatric formulations. This approach is however not very successful for highly bitter and highly water soluble drug. Besides taste masking, this approach is also used to improve the aesthetic appeal of product especially to make it more attractive. In liquid formulations, water-soluble flavors are added to the aqueous component of a formulation, whereas poorly water-soluble flavors are added to the alcoholic or other

non-bitter solvent component of the formulation. Fruit flavors are often used to mask sour taste, whereas bitter tasting drugs are often blended with salty, sweet or sour tasting agents. It is well known fact that salty taste reduces sourness and increases sweetness, whereas sweet taste reduces bitterness. For example, fruity syrups such as raspberry and wild cherry syrups are often used to mask the excessive sour taste of a medicament.

b. Numbing of taste buds.[28, 29, 30]

Temporary numbing of taste buds by certain anesthetizing agents such as phenol and sodium phenolate has also been used to mask the unpleasant taste of drugs such as aspirin. Swabbing of the gingiva in the oral cavity with a topical anesthetic has been shown to temporarily reduce the bitter taste of the dental anesthetics, which often leak into the oral cavity after an injection. Clove oil has been found to be a good taste masking component for a number of medicinals because of its spicy and anesthetic effect on taste buds. To support taste-masking capabilities of clove, vanilla flavor are preferred.

6.2 Chemical approaches[31, 32]

a. Prodrugs: Silyated compounds of erythromycin have markedly superior taste when compared to their corresponding parent compounds. It is believed that the silyated compounds of the antibiotics function as prodrugs releasing parent antibiotic in vivo. Clindamycin is an extremely bitter semi synthetic antibiotic. To improve its pharmaceutical acceptability, four clindamycin-2- acetyl esters of varying chain lengths, namely palmitate, laurate, hexanoate, and acetate were synthesized.

b. Preparation of salt: In general, this approach is made to modify the solubility of the drugs. Sometimes the drugs are converted into particular salt to modify their taste. Megulumine, an acid addition salt of Ibuprofen, increases not only solubility of ibuprofen but also provide significant taste masking effect. Erythromycin can be made practically tasteless and odorless by preparing estolate salt.

6.3 Barrier approaches.

a. Coating by Wet Granulation[33, 34, 35, 36, 37]**:** This process may be described as one, which agglomerates drug particles through a combination of adhesion and cohesion using a wetting agent and binder. This method consist of the mixing of the ingredients in a solids-liquid processor to form a dampened, agglomerated mass that may be then subdivided, dried, and sized to form a suitable free-flowing and compressible granules. Although this process is primarily intended to impart flow ability and compressibility to impalpable substances, under

certain conditions it may be useful in the application coatings to drug particles in order to mask or reduce their bitter taste. In general, this is the simplest approach to taste masking.

b. Viscosity modifier[37, 39,41, 42]**:** In this technique, aqueous dispersions of natural gums such as acacia, tragacanth, xanthan, etc. or semisynthetic/syntheic polymers such as sodium carboxymethyl cellulose, polyethylene glycols, hydroxy propyl methyl cellulose, hydroxy propyl cellulose, etc are used to increase the viscosity, which limits the contact of unpleasant tasting drugs with taste buds. Acetaminophen suspensions can be formulated with xanthan gum (0.1-0.2%) and microcrystalline cellulose (0.6-1%) to reduce bitter taste. Combination of polyethylene glycol and sodium carboxy methylcellulose were used to mask the unpleasant taste of drugs such as Pseudoephedrine HCl, Dextromethorphan etc.

c. Emulsions [1, 40, 43]**:** The single as well as multiple emulsions are helpful in masking the taste of medicament. The use of multiple emulsions for masking the bitter taste of Chloroquine was investigated in O/W/O and W/O/W emulsion systems. The results indicated that the O/W/O systems could mask the taste of Chloroquine to some extent. Mineral oil, is used as a lubricating cathartic, have an unpleasant taste to be taken orally. The formulation of O/W type of emulsion markedly improves its palatability.

d. Lipid vesicles[24, 44, 45]**:** Another way of masking the unpleasant taste of drug is to entrap the drug into lipid vesicles, liposomes. Incorporating them into liposome prepared with egg phosphatidylcholine can mask the bitter taste of an antimalarial drug, Chloroquine Phosphate.

e. Microcapsules / Microspheres[30, 31, 36]**:** Micro capsulation involves coating of drug particles using a natural or synthetic polymer or wax. Several techniques such as coacervation separation, solvent evaporation, spray drying, spray congealing, fluidized bed coating, etc. have been used. Encapsulating in the mixture of gelatin and acrylic polymers such as eudragit L-100, S-100, and E-100 masked the unpleasant taste of the Clarithromycin. Such encapsulated drugs can be successfully formulated as a suspension.James et al masked the bitter taste of Cefuroxime axetil by coating with lipids which get dispersed on contact with gastrointestinal fluid.

6.4 Complexation and adsorption

a. Adsorbate Formation[24, 30]**:** Drug-substrate adsorbate can be prepared by two methods: Solvent method and Melting method.

1) Solvent Method: Generally the formation of an adsorbate involves dissolving the drug in a solvent, mixing the solution with the substrate, and evaporating the solvent, leaving the

drug molecules adsorbed upon the substrate. The variables of the process, such as choice of solvent, substrate, proportions, mixing conditions, rate of evaporation, and temperature, must be optimized to give the desired product.

2) Melting Method: In this method, the drugs and a carrier are melted together by heating. The melted mixture is then cooled and rapidly solidified in an ice bath with vigorous stirring. The product is then pulverized and sized. Heat labile drugs, volatile drugs and drugs that decompose on melting are unsuitable for this method. The method is simple with low cost and no problem of residual solvents as are encountered in the solvent evaporation method.

b. Inclusion Complexation[44, 46, 47, 48]: In the inclusion complex formation, the drug molecule (guest molecule) fits into the cavity of complexing agent (host molecule) forming a stable complex. The complex is capable of masking the bitter taste of the drug by both decreasing the amount of particles exposed to the taste buds and/or by decreasing the drug solubility on ingestion, both activities leading to a decreasing bitterness of the drug. The forces involved in inclusion complexes are usually of the Vander-Waals type and most widely used complexing agent in inclusion complexes is B - cyclodextrin, a sweet, nontoxic, cyclic oligosaccharide obtained from starch. Three primary methods have been reported for the preparation of cyclodextrin inclusion compounds:

1) Equimolar quantities or a tenfold excess of water-soluble substances, are dissolved directly in concentrated hot or cold aqueous solution of the cyclodextrin. The inclusion compounds are crystallized out immediately or upon slow cooling and evaporation.

2) Water insoluble drugs are dissolved in a non-water-miscible organic solvent and shaken with a concentrated aqueous solution of cyclodextrin. The inclusion compounds crystallize at the interface between the layers, or as precipitate. The crystals must then be washed with solvent to remove uncomplexed drug and dried under appropriate conditions to remove residual solvents.

3) The drug substance is added to the cyclodextrin and water to form slurry, which undergoes an increase in viscosity with continuous mixing. This may be concentrated to a paste that can be dried, powdered, and washed.

c. Taste Masking by Ion-Exchange Resins (IERs) [49, 50, 51]: Ion-exchange resins (IERs) are high molecular weight polymers with cationic and anionic functional groups. Ion-exchange resins are used in drug formulations to stabilize the sensitive components, sustain release of the drug, disintegrate tablets, and mask taste. Drug can be bound to the resin by either

repeated exposure of the resin to the drug in a chromatographic column or by prolonged contact of resin with the drug solution. Drugs are attached to the oppositely charged resin substrate, forming insoluble adsorbates or resinates through weak ionic bonding so that dissociation of the drug-resin complex does not occur under the salivary pH conditions. This suitably masks the unpleasant taste and odor of drugs.

7. Evaluation of taste masking:

As we all know that the medicines are the only way for human beings to get well from the disease. But these medicines are not always compatible, they have to make it, by incorporating an agent which can improve the palatability of these medicaments and provides the patient with a pleasant product experience.[52] Sensory analysis has been used in developed countries for years to characterize flavors, odors, and fragrances. Historically experts provided formulation scientist with subjective data on the composition of one product with another. Soutakagi, *et al.* invented a multichannel taste sensor whose transducer is composed of several kinds of lipid/polymer membrane with different characteristics, which can detect taste in manner similar to human gustatory sensation.[48]

A. Human Panel Method:

In this method the taste masked sample is subjected to sensory evaluation by a panel of six to nine members with respect to bitter taste. The evaluation would be performed by classifying bitter taste into following five classes.

Level 5: Very strongly bitter taste is sensed.

Level 4: Strongly bitter taste is sensed.

Level 3: Moderately bitter taste is sensed.

Level 2: Slightly bitter taste is sensed.

Level 1: No bitter taste is sensed.

The pure drug without complexation should be used as a control having an average bitterness value of 5. A written consent of the members of the panel should be taken and explained the procedure involved in testing the taste of complexes. Each of the members is provided with the control that is the pure drug and would ask to compare the bitterness of each of the ratio of complex with that of the control and indicate the level of bitterness perceived by them. The members of the panel would ask to gargle for complete removal of taste sense of previous samples and then the next sample would be given for taste analysis. The average bitterness value of each of the ratio should be worked out based upon the level of bitterness perceived by individual member of the panel.[53]

B. Evaluation using Electronic tongue:

The main elements of an electronic taste sensing system are a different number of various sensor types which can be attached to a robot arm, a sample table, an amplifier and a computer system for data recording. Fig 7.1 shows a rough sketch of the basic principle of electrochemical taste sensing. Basically, these systems try to represent and imitate what is happening while molecules with specific taste properties interact with taste buds on the human tongue. The taste buds are represented by sensors which interact with these molecules at the surface initiating changes in electric potentials. These signals, which can be compared to physiological action potentials, are recorded by a computer system, which corresponds to the neural network at the physiological level. The obtained data can be evaluated afterwards on the basis of an already existing matrix of sensor responses which is comparable with the human memory or association to already known taste patterns. For most of the systems, during analysis, sensors are immersed in samples which are located on an auto sampler and voltage values (mV) are recorded over a specific time period followed by a washing step and measurement of the next sample.[54]

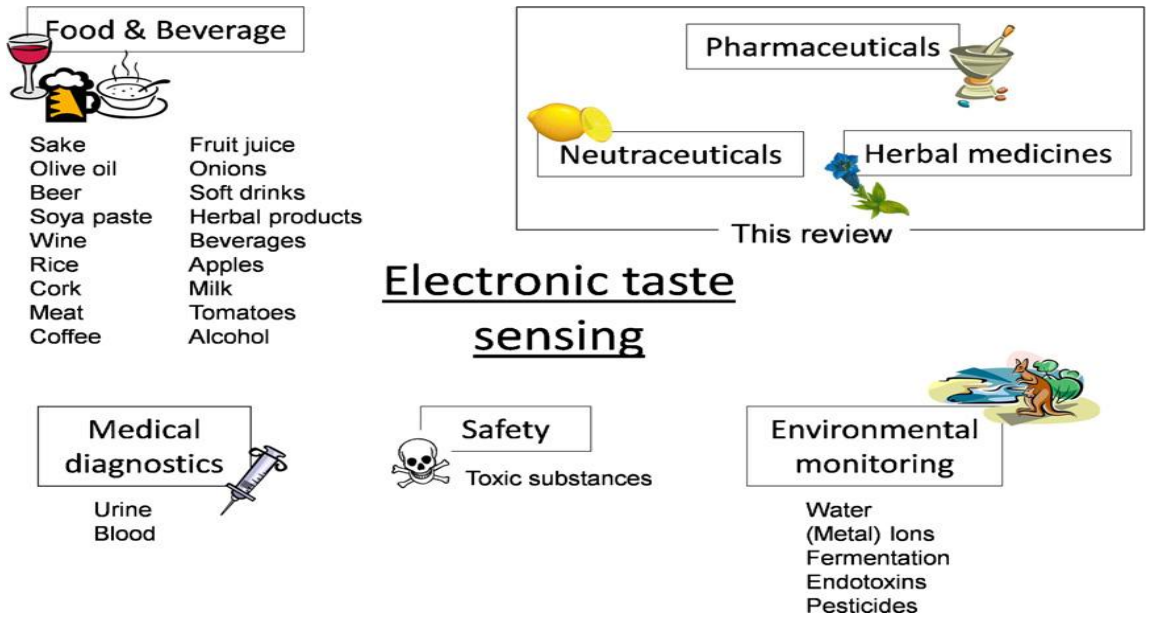

Fig.7.2 Fields of application for electronic taste sensing systems

8. Challenges in developing taste masked formulations for Paediatrics

The taste of a pharmaceutical formulation has major influence on the adherence of a patient to the medication. Children, whose sense of taste is not finally developed yet, might refuse taking unpleasant tasting medicine. Children are more sensitive to bitter tasting substances compared to adults as, from an evolutionary point of view, bitter taste of substances is often associated with toxic attributes. This sensitivity decreases during development and also due to adaptation to such substances. In fact, many active pharmaceutical ingredients have an unpleasant taste, like bitterness, saltiness, or sourness or cause an irritating mouth feeling, like astringency, metallic or spicy taste. For these reasons, taste masking and taste testing have become important topics for the development of a pharmaceutical formulation. Taste is the most important factor governing the acceptability by the child of oral dosage forms. Unpleasant tasting APIs do not usually give rise to problems when formulated as solid oral dosage forms as the dosage form is film or sugar-coated and can be swallowed intact. However, palatability may need improvement in some tablets, i.e. effervescent, soluble and dispersible tablets that are intended to be dissolved or dispersed in water before swallowing; and chewable tablets and tablets to be placed in the mouth (buccal tablets, sublingual tablets). Taste masking and flavouring of liquid oral dosage forms are highly important for a child's acceptance of the medicine and hence for compliance, even in cases where the adult patient would accept the non-taste-masked medicine. During early development of new drugs intended for the oral route of administration, the main emphasis is on suitability of compound properties for adult dosage forms, with the intention of developing tablet or capsule formulations. Although solid dosage forms are widely accepted by older children and adolescents, younger children and their carers tend to prefer liquid formulations. However, many drugs are extremely bitter, and as a result of the above, taste is later often found to be unpleasant during the development of paediatric dosage forms. [54, 55]

The World Health Organization (WHO) published 4th Essential Medicines List (EML) for Paediatrics in April 2013 and according to it about 40 % of paediatric medicines have bitter taste which creates hurdle in the formulation and taste assessment. Indian Academy of Paediatrics in collaboration with World Health Organization published 1st List of Essential Medicines for Children of India in October 2011 which also covers the bitter medication given via oral route.[57]

Certain in vitro and in vivo taste prediction techniques such as the electronic tongue technology and animal models have shown some early promise and optimization of these techniques should be encouraged. Assessing the taste properties of drugs at an early stage could facilitate later stage drug product development activities. In addition, the molecule's solubility characteristics may not be ideal for the liquid dosage form approaches preferred by young children. Compounds with high solubility can be difficult to taste mask in liquid preparations, as they often cannot be easily formulated as suspensions. Even suspensions of poorly soluble compounds can exhibit poor palatability characteristics if the small amount of solubilised drug exceeds the human taste threshold, or if mouth feel is compromised by the suspended drug substance. Taste masking of certain solid paediatric dosage forms such as chewable tablets or fast dissolving preparations (e.g. orodispersible tablets and films) can also be challenging, especially for high solubility drugs which may dissolve rapidly in the mouth. Alternative approaches to facilitate taste masking of paediatric solid preparations include coating of drug substance prior to incorporation into formulations, or film-coating of small dosage forms such as pellets or mini tablets. Masking the taste of drugs whilst retaining the original pharmacokinetic profile for the dosage form of choice can also be challenging. Some taste masking approaches such as binding of the drug to ion exchange resins or use of prodrugs or alternative salt forms may alter a drug's in vivo performance.[54]

In order to determine whether the available masking technique is effective, different approaches are available. Human taste panels, animal models or analytical techniques are commonly used. But, determination of taste masking efficiency by human taste panels reveals challenges with respect to possible toxicity of the drug. This is especially true for new chemical entities, which often have unknown toxicity status. Further, taste assessment by human beings is affected by differently developed senses of taste and individual preference and intra individual variations. Even if a trained and calibrated panel is used, evaluation of taste is susceptible to physical and physiological conditions. In children both limitations play a major role. Ethical concerns inhibit taste studies in children and in addition younger children have difficulties to give valid statements. Animal models might be valid, if the medication is intended for veterinary use, but they are hardly representative for human taste sensation. Therefore, analytical techniques were used in the past as for example dissolution testing and detection of the free amount of drug via UV spectroscopy. With this approach only single substances can be detected. To investigate multi-component mixtures, such as

oral liquid formulations, these methods can hardly be applied. Electronic sensor array systems, so called electronic tongues, offer an alternative to characterize the taste masking efficiency for multi-component formulations. These systems have attracted increasing attention over the last years. They were initially implemented in the food sector, but are also used for pharmaceutical purposes.[56]

Taste sensing systems are analytical sensor array systems which are able to detect specific substances by means of different artificial membranes and electrochemical techniques. There are various synonyms for these sensor array systems as for example taste sensor, taste chip, taste sensing system, electronic sensor array system, biomimetic sensor array system or electronic tongue. Electronic taste instruments have been developed and optimized to answer some of these issues: reduces human sensory test panels, precise measurement of taste, requires small sample volume, decreased measurement time, small size of sensor, reproducibility, easily operated by unskilled personnel. An electronic tongue is a sensor that works on the liquid samples. The responses of the sensor are not specific. The collective response of the tongue sensor varies from solution to solution due to the presence of different compounds and ions. Electronic tongue sensor, in general, makes use of this collective response, and various electrochemical methods have been exploited for such analysis. Potentiometry, Voltametry, and conductometry are some of the measurement techniques that have been used successfully in electronic tongues for different applications.

The main elements of an electronic taste sensing system are a different number of various sensor types which can be attached to a robot arm, a sample table, an amplifier and a computer system for data recording. The taste buds are represented by sensors which interact with sample molecules at the surface initiating changes in electric potentials. These signals, which can be compared to physiological action potentials, are recorded by a computer system, which corresponds to the neural network at the physiological level. The obtained data can be evaluated afterwards on the basis of an already existing matrix of sensor responses which is comparable with the human memory or association to already known taste patterns. For most of the systems, during analysis, sensors are immersed in samples which are located on an auto sampler and voltage values (mV) are recorded over a specific time period followed by a washing step and measurement of the next sample. Two systems are already commercially available, the Insent taste sensing system and the Astree electronic tongue. In addition, various laboratory prototype versions also exist.[54, 55, 56]

9. CONCLUSION

Taste masking is valuable strategy to improve patient compliance especially for paediatrics. So many methodologies have been adopted for masking the bitter taste. Use of sweetners is an age old and most popular tool but novel methods have explore the attention towards pharmaceutical companies. With the ongoing advancements, using various technologies future looks more promising for pharma industry.

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