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Review on taste masking approaches in oral pharmaceutical dosage forms

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ABSTRACT

The majority of active pharmaceutical ingredients (APIs) found in oral dosage forms have unpleasant or obnoxious taste including, bitter, sour, salt, sweet and umami tastes. Taste is now one of the most important factors influencing the quality of the product, hence therapeutic value, compliance, and acceptance of the patient.

Masking the unpleasant taste of active pharmaceutical ingredients (APIs) is a major challenge in the pharmaceutical oral dosage form design and in the development of such oral dosage forms, especially those used for pediatric patients. The desire of improved palatability in these products has prompted the development of numerous formulations with improved performance and acceptability. This reason is an initiative for the development of various taste masking technologies by which the characteristics of the dosage form is improved and good patient compliance is achieved. The present article reviews the earlier applications and methodologies of taste masking and discusses the most recent developments and approaches of bitterness reduction and to give an idea about the traditional and recent taste masking evaluation techniques whereby, increasing palatability for oral pharmaceuticals.

Key Words: Bitter drugs, Patient compliance, Taste masking techniques, Taste assessment.

INTRODUCTION

Taste sensation is the ability to detect the flavor of substances like food, beverage products, and drugs. Taste is now one of the most important parameters governing the patient compliance[(1)]. Orally administered drugs are provided to the patient in many dosage forms, including solid forms such as capsules, tablets, and granules and liquid forms such as solutions or suspensions. Conventional tablets and capsules are usually intended to be swallowed whole and taste masking not need to be considered in their formulation, because in case of tablet; the drug is coated with tasteless film coat or sweet sugar coat and in capsules; the drug is enclosed within tasteless gelatin shell. Children, older persons, and many other persons including disabled patients often have trouble swallowing tablets or capsules. In these situations, it is desirable to provide the drug either in a dissolvable solid form or as a liquid form. However, a common problem associated with liquid pharmaceutical dosage forms is the often disagreeable taste of a drug. Improve palatability desire of these products has prompted the development of numerous formulations with improved performance and acceptability. The approaches most commonly involved for achieving taste masking include various chemical and physical methods, these methods aimed to masking or to prevent drug taste buds interaction [(2)]. The simplest methods involve the use of flavor enhancers. if these methods fail, more complex approaches are adopted. Various techniques have been identified for taste masking which include polymer coating, formulation of inclusion complexes, use of ion exchange resins, prodrug technology, liposome, microencapsulation, multiple emulsions, use of anesthetic agents, salt preparation, granulation, adsorption, use of lipophilic vehicles, effervescent agents, freeze drying process, rheological modifiers, gel formation, solid dispersion systems, polymer coating, wax embedding drug, pH-modifier, and mass extrusion method[(3)]. The present review attempts to give a brief account of traditional and recent technologies of taste masking with respect to dosage form along with various methods of evaluation of taste masking effect. Two approaches are commonly utilized to overcome bad taste of the drug. The first includes reduction of drug solubility in saliva, where a balance between reduced solubility and bioavailability must be achieved. Another approach is to alter the ability of the drug to interact with taste receptor.

The sense of taste

The taste can be defined biologically as the chemical reaction arising from responses of the four main traditional taste perceptions: sweet, salt, bitter and sour and the recently discovered fifth basic taste umami, the taste of certain amino acids (e.g. glutamate, aspartate and related compounds) which is identified by Kikunae Ikeda in 1909. The main function of the taste is to drive the appetite for the body requirements such as sugars and proteins and to protect us from poisons-"gatekeeper to the body" [(4)].

Anatomy and distribution of taste

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Humans receive tastes through sensory organs, taste buds, (also known as gustatory calyculi) concentrated on the upper surface of the tongue. Taste bud is onion like shape and opens into epithelial surface through a small opening called taste pore. In mammals, taste buds are groups of 30-100 individual elongated "neuroepithelial" cells, which are surrounded in exclusive structure in the adjacent epithelium, termed taste papillae (Fig. 1)[3]. At the apex of the taste bud, Microvilli protrudes from the taste pore arising from the individual taste cells into the oral milieu. Just below the taste bud apex, taste cells are joined by tight junctional complexes that prevent gaps between cells. Food molecules cannot therefore squeeze between taste cells and get into the taste bud. Taste papillae can be seen on the tongue as little red dots, particularly at the front of the tongue. There are four types of these papillae and each has its own specialized function. The four different types are filiform, fungiform, circumvallate, and foliate. Figure 1 shows the four types of taste papillae. Taste buds are situated on the taste papillae. At the base of the taste bud, afferent taste nerve axons invade the bud and ramify extensively, each fibre typically synapsing with multiple receptor cells within the taste bud. In mammals taste buds are located throughout the oral cavity, in the pharynx, the laryngeal epiglottis and at the entrance of the esophagus[4].

Physiology of taste

Physiologically, taste is a sensory response resulting from a chemical stimulation of receptor cells on taste buds[5]. The receptor cells are of two types functionally. One is ion channel type receptor which allows the ions that give rise to sensation of salt and sour. The sense of taste is conducted to the brain as chemical signals resulting from the ionic interactions which causes electrical changes within the taste cells. Tastants alter the net negative charges of the taste cells causing increase in positive ion concentration within the taste cells which lead to depolarization and release of neurotransmitters[3].

The other is a surface protein receptor which allows binding of tastants by a taste transduction process and give rise to sensation of sweet, bitter and umami. In case of bitter taste, the stimuli acts the binding between the tastants and G-protein coupled receptors in the cells, triggering the release of a G-protein called gustducin[3]. Taste sensation begins when gustducin activates the effector enzymes phosphodiesterase 1A. The effector enzymes then change the intracellular levels of second messengers such as cyclic adenosine monophosphate (cAMP), which release the calcium ions from endo plasmic reticulum of the taste cell. The second messengers also activate sodium, potassium and calcium channels on the extracellular membrane. This ionization depolarizes the cell, causing the release of neurotransmitters that send a nerve impulse to the brain that carries the signal of taste. The resulting sensations are transmitted to the brain by the ninth cranial nerve and tastes are detected. The sensitivity of the tongue to different sensation is affected by the age and is varies widely among individuals[6].

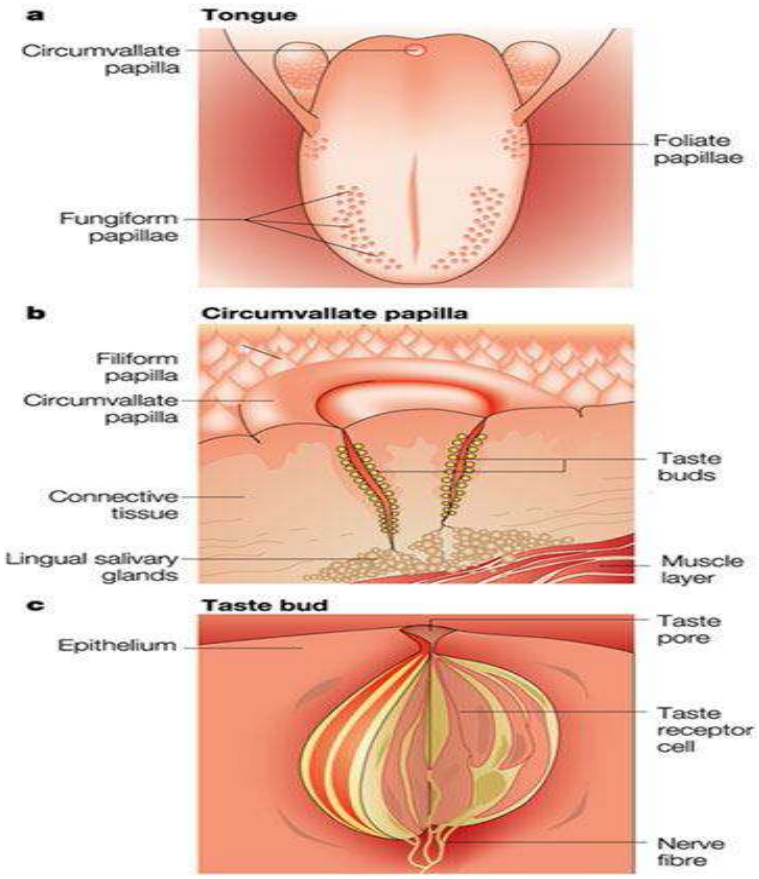

Fig. 1: Structure of taste bud[3]

DESCRIPTION OF FUNDAMENTAL TASTE SENSATIONS

Taste sensations can be classified into five principle tastes: sweetness, sourness, saltiness, bitterness, and umami. Umami is a Japanese word that can be translated roughly as "a pleasant savory taste" or meaty Taste. Umami is specifically the taste created by the presence of glutamates and nucleotides.

The taste of substances is correlated to the chemical structure of their compounds, for instances,

low molecular weight salts tend to taste salty where as high molecular weight salts tend toward bitterness. Nitrogenous compounds, such as alkaloids, tend to be quite bitter. Organic compounds containing hydroxyl groups tend to become increasingly sweet as number of OH group increases[7]. Four basic taste are confirmed to specific regions of tongue (Table 1). But some workers deny the presence of specific regions of the tongue for a particular taste and consider it as a misconception. Threshold for taste is a minimum concentration of a substance that evokes perception of taste. The following table 1 gives the threshold concentration of four primary taste sensation[7].

Table 1 Specific area of tongue and threshold concentration for primary taste sensations[7]

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

Taste masking

Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist. Taste masking technologies are very important for improving patient compliance and better therapeutic efficacy. Taste masking technology includes two aspects:

- Selection of suitable taste masking substance.
- Selection of suitable taste masking techniques.

A suitable taste masking technique can powerfully impact both, quality of taste masking and process effectiveness[5].

Factors affecting selection of taste masking technology[8]

1) Extent of the bitter taste of the API.
2) Required dose load.
3) Drug particle shape and size distribution.
4) Drug solubility.
5) Desired release profile and desired bioavailability.
6) Required dosage form.
7) Required disintegration and dissolution rate of the finished product.

Properties of an ideal taste masking process[9]

1) No adverse effect on drug bioavailability.
2) Involve least number of equipment and processing steps.
3) Least manufacturing cost and easy to prepare.
4) Can be carried out at room temperature.
5) Require minimum number of excipients that are safe, have lower cost and easily available.

Taste masking techniques:

Broadly, approaches to taste masking aim to use strong flavours, maskers and sweeteners to overpower the bitter Active Pharmaceutical Ingredient (API), reduce contact between the API and the taste buds, or to reduce release of the API in the oral cavity[10]. To achieve the goal of taste abatement of bitter or unpleasant taste of drug. Various techniques reported in the literature are as follows[11]

1. Addition of flavoring and sweetening agents.
2. Microencapsulation.
3. Granulation.
4. Ion exchange resins.
5. Formulation of inclusion complexes.
6. Bitterness inhibitors.
7. Multiple emulsions.
8. Prodrug approach.
9. Gel formation.
10. development of liposomes.
11. Miscellaneous.

1. Addition of flavoring and sweetening agents.

This technique is the foremost and the simplest approach for taste masking, especially in the case of pediatric formulations, chewable tablets, and liquid formulations. But this approach is not very successful for highly bitter and highly water soluble drugs. Artificial sweeteners and flavors are generally being used along with other taste-masking techniques to improve the efficiency of these techniques. Flavours are classified into natural and artificial (table 2). Selection of suitable flavouring agent to be added depends on the original sensation of drug substance (table 3). Examples of various classes of drugs of which the taste masking is achieved by the use of sweeteners and flavouring agents are listed in (table 4).

Table 2: Classification of flavouring agents[3, 12]

Type	Example	Significance
Natural	Peppermint	Less stable
Artificial	Vanilla	Highly stable
Natural and artificial	Strawberry	Effective at low concentration

Table 3: Selection of flavours based on sensation of taste[13]

Sensation	Flavor
Salt	Butterscotch, apple, apricot, peach, vanilla
Bitter	Wild cherry, walnut, chocolate, mint, passion fruit
Sweet	Fruit and berry, vanilla
Sour	Citrus flavours, liquorice, root bear, raspberry

Table 4: Taste masking with flavours, sweeteners, and amino acids[10].

Drug(s)/active agent(s)	Type of formulation	Taste masking agent(s)
Eucalyptus oil	Mouth washes	Fenchone, borneol or isoborneol
Benzelthonium chloride	Dentifrices	Stevia-based sweetener extract and glycerin
Zinc acetate dihydrate	Lozenges	Anethol-b-cyclodextrin complex and saccharin
Aspirin	Effervescence tablets	Sodium phenolate
Thymol	Oral rinses	Anethole, eucalyptol, and methyl Salicylate
Theophylline	Elixirs	sodium saccharin, sodium glutamate, and vanilla
Chloropheniramine	Solution	Sodium bicarbonate, citric acid, and orange flavor
Ibuprofen	syrup	Sodium saccharin, and refined sugar
Famotidine	Solution	Sodium bicarbonate, citric acid, and lemon flavor
Acetaminophen	Suspensions	Sodium bicarbonate, citric acid, and cherry flavor

2. Microencapsulation.

Microencapsulation is a process in which the active moiety (solid or liquid droplets) is coated with a polymeric material or film. It is important to understand that only soluble portion of drug can generate the sensation of taste, and it is possible, or even likely, that coating the active drug with a properly selected polymer film can reduce its solubility in saliva and taste could be masked. Coating the drug particles created a physical barrier between the drug and the taste buds and the taste of active could be masked. Microencapsules are made up of a polymeric skin or wall enclosing a core[14, 15].

Table 5: Taste masking of bitter drugs by microencapsulation[12]

Technique	Drug	Coating agent	Dosage form
Spray drying	Ampicillin trihydrate	Sodium CMC	Powders
Spray congealing	Clarithromycin	Glyceryl monostearate	powders
Coacervation Phase separation	Chloroquine diphosphate	Eudragit RS100	powders
Solvent Evaporation	Metronidazole	Eudragit E, Fattybase	Suspension

Polymers used for coating in microencapsulation should have the possibility to mask the taste of bitter drug and not adversely affecting the drug release profile[16]. To attain a balance between the taste masking and release drug profile, combinations of pH independent water insoluble polymers such as cellulose ethers, cellulose esters, polyvinyl acetate and water soluble polymers such as cellulose acetate butyrate, polyvinylpyrollidone, hydroxyethyl cellulose have been used[17]. Other coating agents employed in microencapsulation are gelatin, povidone, HPMC, ethylcellulose, carnauba wax, acrylics and shellac[10].

Methods used to prepare microencapsules are air suspension coating, coacervation- phase separation, spray drying and spray congealing, pan coating, solvent evaporation and multiorifice centrifugation method[18]. In literature some of the mentioned techniques of microencapsulation have been reported for taste masking purpose, as shown in table 5.

3. 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. The advantages of this technique are less expensive, rapid operation and an easily scalable taste masking technology. Granulation lowers the effective surface area of the bitter substance that come in contact with the taste buds on the tongue upon oral intake[17]. Liquid and low melting point waxes such as glycerol palmitostearate, glyceryl behenate and hydrogenated castor oil are commonly used ingredients during the granulation to achieve taste masking. Some saliva insoluble polymers can also act as binding agents, granules prepared from these polymers show less solubility in saliva and thus taste could be masked. The taste masked granules can also be formulated as chewable tablet and rapidly disintegrating tablets[19, 20]. Table 6 gives the literature report on list of drugs whose taste is masked by granulation techniques by using saliva insoluble polymers.

Table 6: Literature report on taste masking by granulation[3]

Drug	Category	Granulating agent used
Erythromycin	Macrolide antibiotic	Alginic acid
Dextromethorphan	Antitussive	cyclodextrin
Norfloxacin	Flouroquinolone antibiotic	Methacrylic acid ester
Ibuprofen	Anti-inflammatory	Micro Crystalline Cellulose(MCC)
Levofloxacin	Flouroquinolone antibiotic	Castor oil, sugar alcohol
Vitamins	Diet supplement	Polyglycerol ester of polyvalent fatty acids

4. Ion exchange resins (IER).

One of the popular approaches in the taste masking of bitter drugs is based on ion exchange resins. IER have received considerable attention from pharmaceutical scientists because of their versatile properties as drug delivery vehicles. In past few years, IER have been extensively studied in the development of Novel drug delivery system and other biomedical applications. Ion exchange resins are synthetic inert organic polymers consisting of a hydrocarbon network to which ionisable exchange their labile ions for ions present in the surrounding medium[12]. The most frequently employed polymeric network is a copolymer of styrene and divinylbezene (DVB). Apart from this other polymers such as those of acrylic and methacrylic acid crosslinked with divinyl benzene and containing appropriate functional groups, have been used as ion exchange drug carriers [21, 22].

Drug can be bound to the resin by either repeated exposure of the resin to the drug in a chromate graphic column or by prolonged contact of resin with the drug solution. Drugs are attached to the oppositely charged resin substrate, forming insoluble adsorbates or resonates through weak ionic bonding so that dissociation of the drug-resin complex does not occur under the salivary pH conditions[10]. This suitably masks the unpleasant taste

and odor of drugs. Drug release from the resin depends on the properties of the resin and the ionic environment within the gastrointestinal tract (GIT). Drug molecules attached to the resin are released by exchanging with appropriately charged ions in the GIT, followed by diffusion of free drug molecule out of the resins[10].

Ion exchange resins are classified as either anionic or cationic exchangers. Within each category, they are classified as strong or weak, depending on their affinity for capable counter ions table 7. Examples of drugs taste masked by ion exchange resin are summarized in table 8.

5. Formulation of inclusion complexes.

Inclusion complex is a 'host-guest' relationship in which the host is complexing agent and guest is the active moiety (drug molecule). The drug molecule fits into the cavity of a complexing agent i.e., the host molecule forming a stable complex[24]. The complexing agent is capable of masking bitter taste either by 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. Vander Waals forces are mainly involved in the interaction between the host and guest molecules to form the inclusion complexes. b-cyclodextrin is the most widely used complexing agent for inclusion type complexes[6]. Examples of various complexing agents used for taste masking of bitter drugs are listed in table 9.

6. Taste masking by bitterness inhibitors

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 inhibits 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, sodium gluconate 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[12].

Table 7: Common ion exchange resins[12]

Type	Functional group	Polymer backbone	Commercial resins
Strong anion	$-N+R_3$	Polystyrene- DVB	Amberlite IR 400, Dowex 1
Weak anion	$-N+R_2$	Polystyrene- DVB	Amberlite IR 4B, Dowex 2
Strong cation	$-SO_3H$	Polystyrene- DVB	Amberlite IR 120, Dowex 50
Weak cation	-COOH	Methacrylic acid-DVB	Amberlite IRC 50, Indion 204,234,

Table 8: Examples of drugs taste masked by ion exchange resin[12, 23]

Drug	Dosage form	Resin used
Chloroquine phosphate	Liquid suspension	Indion cation exchange resin
Ciprofloxacin	Dry suspension	Lewatit CNP
Ephedrine hydrochloride	Liquid suspension	Indion CRP 244/254
clarithromycin	Liquid suspension	Carbomer 934
Dextromethorphan hydrobromide	Dry suspension	Carbomer 934
Ranitidine hydrochloride	Chewable tablet	Amberlite IRP69/88
Paroxetine hydrochloride	Liquid suspension	Amberlite IRP88

Table 9: Examples of drugs taste masked by inclusion complexation[3, 24].

Drug	Category	Dosage form	Complexing agent used
Gymnema sylvestre	Antidiabetic	Oral liquid	Hydroxypropyl β- cyclodextrin
Benexate HCL	Antiulcer	Granules	β- cyclodextrin
Metronidazole benzoate	Antibacterial	Oral liquid	γ- cyclodextrin
Chloroquine phosphate	Antimalarial	Syrup	Tannic acid
Dimenhydrinate	Antiemetic	Chewable tablet	Eudragit S- 100
Zipeprol	Antitussive	syrup	β- cyclodextrin
Hexitidine	Antibacterial	Mouth wash	β- cyclodextrin

7. Multiple emulsions

One of the novel approaches of taste masking is the dissolving or suspending the bitter drug particles in the inner phase of multiple emulsion, either the inner phase is aqueous or oily according to the solubility of the drug substance. These system is mainly used for controlled-release delivery of pharmaceuticals. If the system is physically stable enough for a reasonable shelf life, the formulation could also mask the taste of drug[(14)]. 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[(25)].

8. Prodrug approach

Chemical modification, including prodrug design is an effective method for reducing solubility, and thereby improving taste. prodrugs are defined as therapeutic agents that are inactive moieties but upon biotransformation liberates 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. Bitter tasteless prodrugs of opioid analgesics and antagonists were formulated for improved buccal delivery, when administered as prodrugs; the bioavailability was improved without visible adverse effect[(26)]s. The extremely bitter antibiotics have been the focus of much work in reversible drug modification[(12)] (Table 10).

Table 10: **Prodrug with improved taste masking**[(14)]

Parent Drug	Prodrug with improved taste
Chloramphenicol	Palmitate or phosphite ester
Clindamycin	Alkyl ester
Erythromycin	Alkyl ester
Lincomycin	Phosphate or alkyl ester
Tetracycline	3,4,5-Trimethoxy benzoate salts

9. Taste masking by gelatin

Hydrolyzed gelatin has been found to provide an improvement in taste and mouth feel when incorporated into small amounts in chewable tablets containing ingredients for taste masking. Water insoluble gels formed by sodium alginate in the presence of bivalent metals are also exploited for their taste masking properties[(6)]. Terfenadine mixed with sodium alginate, carrageenan, and macrogol-400 gives a taste-masked formulation. Ibuprofen and sodium alginate mixed in water and added drop wise to an aqueous solution of calcium chloride gives a tasteless and odorless jelly. A gel base confectionary of acetaminophen was developed in order to improve children's compliance in taking the bitter medicine. The gel immediately changes into a jelly after adding a special liquid. It was reported that the bitter taste was completely disappeared in the jelly-formed medication[(10)].

10. development of liposomes

Another way of masking the unpleasant taste of therapeutic agent is to entrap them into liposome. Liposomes are carrier molecules comprising several layers of lipids, in which the bitter drug is entrapped within the lipid molecule. For example, incorporating into a liposomal formulation prepared with egg phosphotydyl choline masked the bitter taste of chloroquine phosphate in HEPES (N-2-Hydroxyethylpiperazine-N'-2)-ethane sulfonic acid) buffer at pH 7.2[(14)]. Bitter substances are commonly hydrophobic in nature hence lipoprotein composed of phosphatidic acid and β- lactoglobulin can mask the target sites for bitter substances on the taste receptor membrane without affecting responses to salts, acids, sugars or sweet amino acids[(12)].

11. Miscellaneous Methods.

By Effervescent Agent

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[(10)]. Recently, effervescent tablets of fentanyl and prochlorperazine were developed to supply these drugs to the oral cavity for buccal, sublingual, and gingival absorption. The formulations contain the drugs in combination with effervescent agent(s) to promote their absorption in the oral cavity and to mask their bitter taste. An additional pH adjusting substance was also included in fentanyl formulation for further promotion of absorption[(27)].

By 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. Gelatin and flavoring materials (chocolate flavor) mask the bitter taste of tannic acid by viscosity effects, when made into a jelly by cooling[(10)]. Acetaminophen suspension can be formulated with xanthan gum (0.1–0.2%) and microcrystalline cellulose (0.6–1%) to reduce bitter taste[(28)]. The bitter taste of a syrup composition comprising of phenobarbital or acetaminophen was masked by using a polyhydric alcohol such as polyethylene glycol or polypropylene glycol with polyvinyl pyrollidone, gum arabic, or gelatin[(29)]. Other commercially available pharmaceutical compounds delivered using the present approach are pseudoephedrine HCl, dextromethorphan, and ibuprofen[(30)].

Wax Embedding of Drug

Tastes masked by embedded granules of ephedrine HCL, Chlorpheniramine maleate, Diphenhydramine HCL were prepared in stearic acid & other waxes[(31)].

Recent approaches and developments in taste masking

Many researchers in the field of pharmaceutics has significant attempts to develop new and effective

methods for masking and evaluating the taste of bitter drugs.

Deepak Kaushik et al[32] developed specific method to mask the taste of the extremely bitter antibacterial clarithromycin using Tulsion-335, an acidic cation ion exchange resin. The resulted complex formulation has a very little or no bitterness with reference to pure drug.

A method of masking unpleasant taste of clarithromycin using a spray-congealing technique has been developed by Yajima et al[33]. Furthermore, Glyceryl monostearate and amino alkyl methacrylate copolymer E (AMCE) were selected as ingredients. The palatability and taste of optimized formulation (CAM: GM: AMCE, 3:6:1) were significantly improved, compared with conventionally coated granules.

Agarwal, Mittal, and Singh[34] formulated high potency adsorbates of Chloroquine phosphate by batch method using a polyacrylic acid ion-exchange resin. Taste evaluation of the adsorbates showed significant masking of the bitterness of the drug.

Morefield and Tongaree[35] formulated a composition that masks the taste of malflavored organic sunscreens with colloidal silicon dioxide. The composition is meant for topical application to the lips or oral cavity.

Shimizu *et al*.[36] developed enteric-coated microgranules for the lansoprazole fast-disintegrating tablet (LFDT). These enteric-coated microgranules have the multiple functions of masking the unpleasant bitter taste, reducing the damage to the enteric layer during the compression process and improving the stability of lansoprazole.

Nouri *et al*.[37] developed a method for manufacturing coated granules with masked taste and instant release of the active principle. Coated granules of Eletriptan, Ibuprofen, and Pregabaline were prepared using a coating polymer (ethyl cellulose), and using suitable a granule disintegrant, a membrane disintegrant, a permeabilizer, a sweetener and an antistatic agent. The resulting coated granules were dried and incorporated into a fast-crumbling multiparticulate-type tablet. The tasting tests performed on the tablets were satisfactory and taste of active principle was not detected in any of the formulations.

Meneaud, Al-ghazawi, and Elder[38] developed a water dispersible formulation of Paroxetine for immediate oral administration. It comprises a dry blend of paroxetine, a water soluble dispersing agent (polyvinyl pyrollidone/calcium carbonate/sodium starch glycolate), and a taste-masking agent (Eudragit L30D55/b-cyclodextrin/ lecithin/Polacrilin K) as a dispersible powder along with flavors and sweeteners.

Jin *et al*.[39] prepared and evaluated fast-disintegrating (FD) tablets of Nicorandil. A FD tablet containing nicorandil-loaded particles with 1% – 4% crosscarmellose sodium in addition to D-mannitol and lactose (9:1) was prepared and examined. The results suggest that the formulation has a masking effect against the bitter taste and irritation of the 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. various techniques of taste assessment are employed as a quality-control parameter for evaluating taste-masked formulations. Both in vitro and in vivo methods can be used to assess a new molecular entity as well as any active substances or formulations.

***In vivo* approaches for taste assessment**

Comprehensive in vivo taste assessment studies are generally performed by applying test samples in which taste needs to be assessed on to the tongues of either humans or animals. The whole physiological process of successful taste masking analysis takes place by an interaction of the stimulus with receptors embedded in the membrane of the taste buds. Receptor–stimulus (ligand) interactions are transduced as an electrical signal followed by a transmission, via the appropriate nerve fibres, to the brain and thus the taste is sensed. Such studies would therefore include panel testing (human subjects) and measurement of frog taste nerve responses(40, 41).

a. Panel testing

The human panel testing is a psychophysical rating of the gustatory stimuli. This method is conducted in a controlled manner, where tastants (foods, chemicals, drugs) are evaluated by estimating the gustatory sensation responses in healthy human volunteers(40). They are sensitive measures of taste and are statistically designed to minimize bias and variable responses within and between human volunteers. 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(16). This method of evaluation is still used up to date as in the evaluation of new antiemetic ondansetron hydrochloride which done between Jan and Mar. 2015(42).

b. 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(16). 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 have been reported to be evaluated by this technique(43).

***In vitro* approaches for taste assessment**

In vivo testing is expensive and subject to ethical considerations and inter-subject variability, therefore in vitro taste assessments are becoming increasingly popular. In vitro taste assessments are indirect methods for assessing taste because the methods do not contribute to the evaluation of taste and sweetness of the drug product itself. Novel dissolution studies of drugs by conventional (dialysis) or pharmacopoeia methods have both been adapted to simulate buccal dissolution of dosage forms and therefore tend to simulate the release of bitter tasting drugs in the mouth[(42)]. Some commonly used in vitro taste assessments methods are discussed below.

a. Multichannel taste sensor / magic tongue

This is an automated taste sensing device to detect the magnitude of bitterness of a drug substance[(16)]. The device has a transducer which is composed of several kinds of lipid/polymer membranes with different characteristics that can detect taste in a manner similar to human gustatory sensation. Taste response is transferred into a pattern composed of electric signals of membrane potentials of the receptor part. Different response electric potential pattern are obtained for substance 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[(44)].

b. Spectrophotometric method

A known quantity of the taste masked formulation is mixed with 10 ml of distilled water in 10 ml syringe by revolving the syringe, end to end, five times in 30 seconds. The test medium is then filtered through a membrane filter, followed by spectrophotometric determination of the concentration of the drug in the filtrate. If this concentration is below the threshold concentration, it may be concluded that the bitter taste would be masked in vivo[(12)]. This technique has been applied to evaluate the taste masked granules of sparfloxacin, with threshold concentration being 100 µg/ml[(45)]. This method also used in the evaluation of drug release from ambroxol hydrochloride resin complex[(46)]. Generally the taste evaluation involves the objective or analytical method and subjective or hedonic method.

Conclusion:

Taste masking practice becomes one of the most crucial factors influencing the therapeutic outcomes especially in paediatric populations. Number of technologies are available not only for masking the objectionable taste of drugs but also to increase the palatability of the formulation whereby, improving product preference to a large extent, increasing the production company profits and creating brand value for the company.

Among the taste masking approaches mentioned in this article**,** is the combination of sweeteners with other taste strategies such as ion exchange resins, bitterness inhibitors, microencapsulation and prodrug formation. This combination is found to be a more efficient strategy. This review also come up with the conclusion that the ultimate goal of recent researches is to get the ideal solution by reduce or inhibit the bitterness and this perhaps could gained by discovering the universal inhibitor of all bitter-tasting substances that does not affect the other taste modalities such as sweetness. However, unfortunately to date such a miracle substance that acts as the universal inhibitor of a bitter taste is not discovered yet.

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