TASTE MASKING IN ORAL DRUG DELIVERY SYSTEMS: A TECHNOLOGICAL UPDATE

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ABSTRACT

Taste is one of the most important aspects of formulation development of oral liquids, disintegrating tablets, chewing tablets or mouth dissolving tablets in terms of patient compliance. Now-a-days there are number of techniques available to mask the bitter or unpleasant taste of drugs. Some of them include coating of drug particles; microencapsulation; molecular complexes of drugs with substances like cyclodextrins or ion exchange resins; formation of solid dispersions, salts or derivatives; use of amino acids and protein hydrolysates and viscosity modification. This review briefly elaborates about sensation and type of tastes and abovementioned taste masking techniques.

Keywords: *Taste masking, microencapsulation, complexation, solid dispersion, prodrug*

Introduction

Drug delivery systems intended to disintegrate within the buccal cavity such as mouth dissolving tables, orally disintegrating tablets and chewable tablets are very popular due to the patient compliance they offer i.e. these dosage forms do not require water for administration. Such dosage forms are even easy to manufacture using the conventional systems of compression. In order to be successful these dosage forms require to fulfill certain organoleptic properties among which taste is a major property. Other types of formulations which require good taste are liquid orals and dispersible tablets. Almost every active pharmaceutical ingredient has an unacceptable taste due to which they are administered along with excipients with pleasant taste. Few drug candidates are so intensely bitter that they require extensive processing to convert them into palatable dosage forms. There are two approaches which are commonly used to overcome bad taste of the drug. The first one 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 present review is a discussion on sensation and type of tastes and, various taste masking technologies currently being used in the development of oral drug delivery systems.

Taste sensation

Taste is one of the most important organoleptic characteristics which results due to chemical stimulation of taste buds located on the surface of the tongue (Fig. 1). About 10,000 taste cells are located on the surface of several papillae, which cover the tongue, palate, epiglottis, and pharynx and help us to determine the flavor of food. Once the taste receptor cells in the taste buds interact with any tastant (soluble food or medicine), they get sensitized and a signal of taste is conducted to the brain by a process called taste transduction.

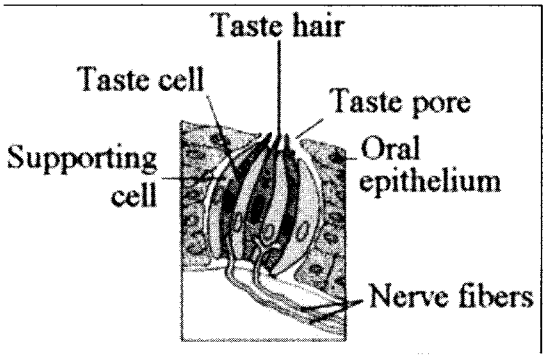

Figure 1: Structure of a taste bud (from ref. 1).

At the cellular level, tastant binds with G-protein coupled receptors in the cells which result in the release of a G-protein called gustducin. The process of taste sensitization begins when gustducin activates the effector enzymes phosphodiesterase 1_A or phospholipase C_{b-2} which in turn change the intracellular levels of second messengers such as cyclic adenosine monophosphate (cAMP), inositol 1, 4, 5 triphosphate (IP_3) and idacylglycerol (DAG). The second messengers activate ion channels which include calcium channels present inside the cell and sodium, potassium and calcium channels

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located on the extracellular membrane. This ionization phenomenon depolarizes the cell resulting in the release of neurotransmitters that send a nerve impulse to the brain by the ninth cranial nerve after which the sense of taste is finally felt (2). This complete process, starting from the contact of the tastant to the taste bud to the formation of signal of taste in the brain, takes a fraction of second.

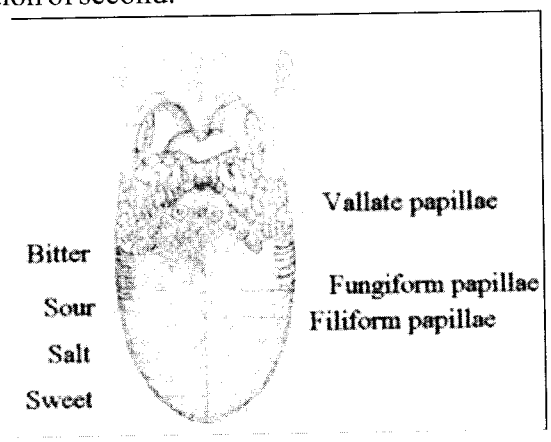

Figure 2: Loculi of different tastes at different parts of tongue (from ref. 3)

The signal of taste elicited by the tongue is interpreted by the brain using four primary taste sensations which include sweet, sour, bitter and salty, depending on the interaction of tastant with the particular type of taste buds. Although the taste buds are distributed all over the tongue, certain areas of the tongue respond more readily to specific tastes than others as shown in fig 2. The tip of the tongue easily identifies sweet sensation, bitterness is identified at the back of the tongue and the salty sensation is detected at the tip as well as at the sides of the tongue. The perception of the types of taste differs widely among individuals depending on the density and distribution of the taste buds on the tongue.

Types of taste

The intensity of any type of taste depends on the solubility of the substance in the salivary fluid. Higher solubility provides greater concentrations of the substance in the solution state at the receptors site accounting for the increased taste sensation.

Sweet: The sensation of sweet taste is exhibited by a wide variety of compounds irrespective of any apparent structural similarity. The two most common sweet substances, sugars and glycerin, are polyhydric alcohols containing $-CH_2OH$ groups, which are responsible to impart sweetness. Saccharin on the other hand has no –OH group but is intensely sweet and has a bitter after-taste. Naturally occurring glycoside and a herbal drug, Glycyrrhiza glabra, is extremely sweet and impart bitterness if used excessively. Some amino acids, e.g. glycine, are sweet. The sodium or calcium salts of cyclohexyl sulfamic acid (cyclamates) and the dipeptide ester aspartame are roughly thirty times sweeter. Compared to sugar, these are required in less quantity due to which they are being widely used as sugar substitutes in the preparation of mouth dissolving tablets.

Sour: The intensity of sour taste depends on the hydrogen ion concentration of the tastant. Therefore, the higher the concentration of hydrogen ions, stronger is the sourness. Chemical substances present in food such as acetic acid (vinegar), citric acid (lemon) and malic acid (apple) are responsible to stimulate sour taste as these acids ionize in aqueous solution to produce hydrogen ions.

Bitter: Many compounds are bitter which are generated mostly due to salts of organic and inorganic compounds. Bitterness is also associated with presence of the nitro or amino groups in a molecule. Structurally unrelated compounds, such as esters of aromatic acids, lactones, and sulfur containing aliphatic compounds exhibit bitterness (2).

Salty: Generally cationic species are partially responsible for the salty sensation. Sodium chloride is typical example of salty taste. Most halide salts (sodium chloride, sodium bromide, potassium chloride and sodium iodide) have a dominating salty taste. Chloride salts of potassium, ammonium and calcium also exhibit salty taste but with a difference. Potassium bromide and ammonium iodide have a salty bitter taste while potassium iodide is intensely bitter, which indicates that the taste sensations of salts shift to bitterness with increase in molecular weight.

Taste-masking techniques

Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist. The ideal solution to reduce or inhibit bitterness is the discovery of a universal inhibitor of all bitter tasting substances that does

not affect the other taste modalities such as sweetness or saltiness. Two comprehensive reviews to control bitter taste have already been reported along with thoughts on the discovery of a universal bitterness inhibitor (4, 5).

Various other techniques available for masking bitter taste of drugs include taste masking with ingredients such as sweeteners and amino acids; and taste masking by: polymer coating; conventional granulation; ion-exchange resin complexation; spray congealing with lipids; formation of inclusion complexes with cyclodextrins; freeze-drying process; making multiple emulsions; and taste masking with gelatin, gelatinized starch, liposomes, lecithins or lecithin-like substances, surfactants, salts, or polymeric membranes. Some of these techniques are described below.

Taste masking by drug particle coating

This process involves the coating of bitter tasting drugs using various inert excipients which would help to prevent the interaction of the drug particles with the taste buds for a considerable period of time. They include starches, polyvinyl pyrrolidones, gelatin, methylcellulose, hydroxypropyl methylcellulose, microcrystalline cellulose and ethyl cellulose. These excipients are either insoluble or take sufficient time to solubilize in the presence of the salivary fluid which helps to provide a physical barrier to the entrapped drug particles. The use of insoluble coat should be restricted to the minimum level sufficient enough to mask the taste as the excess may prevent the immediate and complete release of the drug. The most efficient method of drug particle coating is the fluidized bed coating. In this process, heated and high velocity air is used to fluidize the drug powder in an expansion chamber which gets coated with a coating solution introduced usually from the top through a spray nozzle. The extent of coating to be carried out depends on the solubility of the coating agent in the salivary fluid. The coating thickness can be increased by simply increasing the length of the coating cycle. The quality of air, extent of fluidization, viscosity of coating solution and the rate of spraying are critical parameters which require attention during the coating process.

A preparation of an anti-ulcerative drug, propantheline bromide, was coated using low substituted spherical hydroxypropyl cellulose and further coated with ethyl cellulose to mask the unpleasant taste while readily releasing the active ingredients in the GI tract (6). Taste masking of ibuprofen has successfully been achieved by using the air-suspension coating technique to form microcapsules, which comprise a pharmaceutical core of crystalline ibuprofen and a methacrylic acid copolymer (Eudragit) coating that provides chewable taste-masked characteristics (7).

Taste masking by drug 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, carnuba wax and shellac (8). It differs from the particle coating process on the basis of the techniques used to obtain the drug microcapsules. The method includes coacervation phase separation, spray drying and congealing, solvent evaporation and multi-orifice centrifugation techniques. The unpleasant taste of an antiepileptic drug, beclamide, was masked by microencapsulation followed by tabletting (9). Microencapsulation of the drug was performed using a simple coacervation method using gelatin. Anhydrated sodium sulfate was used as the coaceravating agent. Clarithromycin was microencapsulated using cross-linked gelatin (crosslinking done using glutaraldehyde) and then further coated with either one of the Eudragit resins; L100, S100 and E100. Eudragit E100 was found to be effective in masking the bitter taste of clarithromycin and preventing its release under simulated salivary conditions (10).

Taste masking by drug resin complexation

Taste masking by drug resin complexation is achieved when an ionizable drug reacts with a suitable ion exchange resin, to form a drug resinate complex (11). The complex, by virtue of its insoluble nature in the salivary condition, exhibits no virtual taste due to which even extremely bitter tasting drugs loses their taste when converted into a drug resinate. The selection of ion exchange resin for drug complexation is critical as the drug resinate should be sufficiently stable to prevent break down in salivary fluid and at the same time releases the drug completely under the

gastrointestinal environment (Fig. 3). The drug thus released from resinate gets absorbed in the usual way while the resin passes through the gastrointestinal tract without being absorbed.

Taste masking of intensely bitter antipsychotic drug risperidone using resinate formation was successfully carried out in our laboratory (12). The resinate formation was carried

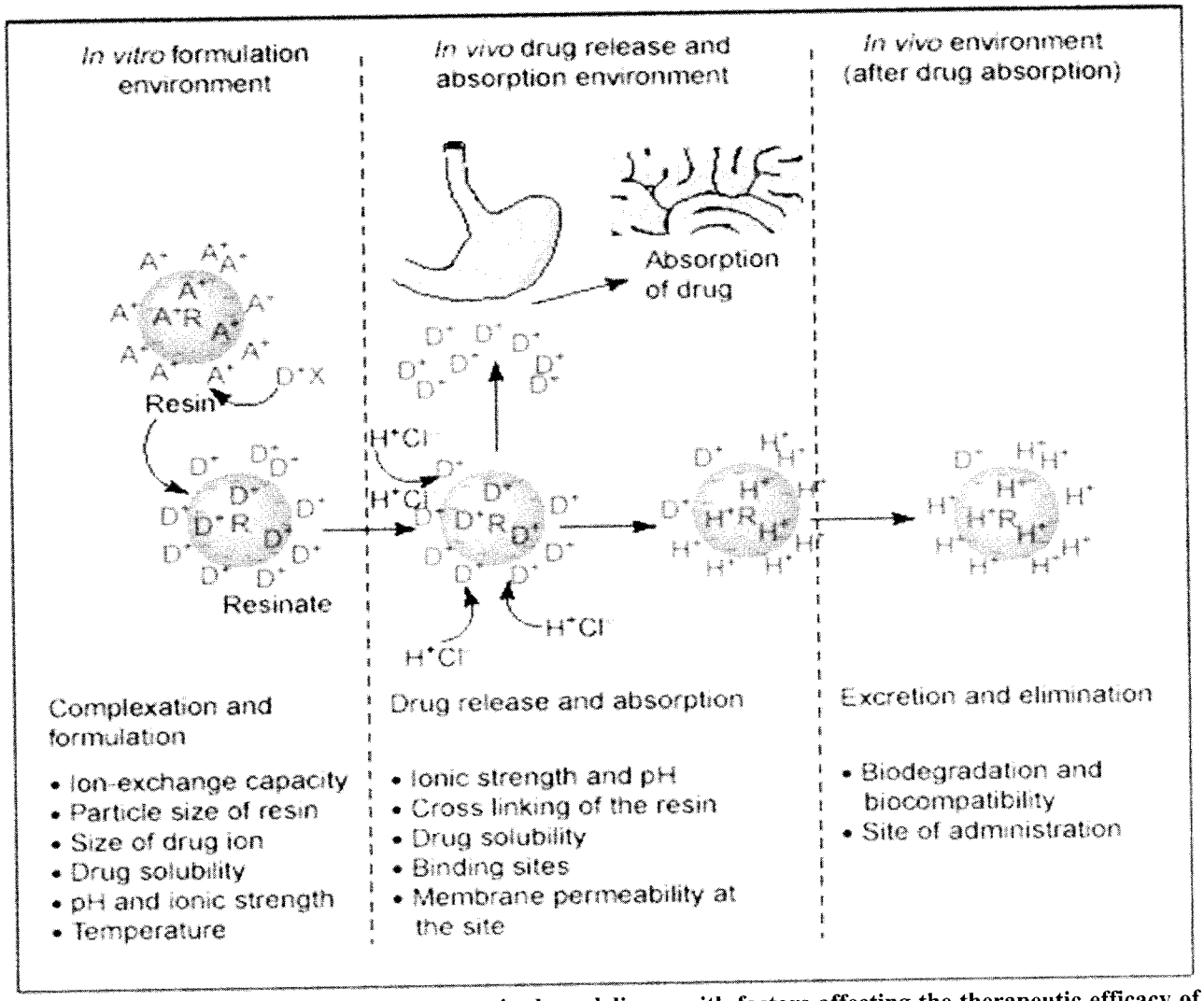

Figure 3: The basis of the ion-exchange process in drug delivery with factors affecting the therapeutic efficacy of the system at each stage. R and a dark circle represents resin; ⁻ sign depicts the integral ion of the resin, and A^- is the counter ion. D^+ is the drug ion, X^- is the ion associated with drug cation and H^+Cl^- is hydrochloric acid. Ions outside and inside the resin indicate ions adsorbed at the surface, as well as at the interior, of the resin structure (from ref. 11).

out using Amberlite IRP64 and effect of various parameters like drug resin ratio, pH of complexation medium, type of complexation medium and time of complexation on drug loading efficiency was studied. It was observed that the maximum loading efficiency achieved was 99.72 ± 0.16 % in 1:4 drug:resin weight ratio at pH 6.0, temperature at 22 °C in a period of 1.5 h using ethanol:water (1:1 ratio v/v) as the complexation medium. Resinate formed was further incorporated into orally disintegrating tablets. Taste evaluation of both resinate and its tablets was done by trained taste panel which confirmed that resinate was tasteless while the fabricated ODTs were having pleasant taste without any trace of bitterness.

Taste masking by drug cyclodextrin complexation

Cyclodextrin is the most widely used complexing agent for inclusion type complexes. It is a sweet, nontoxic, cyclic oligosaccharide derived from starch. The cyclodextrin complexation is a process involving inclusion of the drug molecule within the cavity of cyclodextrin molecule to form

a stable complex. Through encapsulation within the cyclodextrin cavity, molecules or specific functional groups that cause unpleasant tastes or odors are hidden from the sensory receptors. The resulting formulations have no or little taste or odor and are much more agreeable to the patient. This method is most suitable only for low dose drugs. β-Cyclodextrin forms inclusion complexes with organic molecules both in solid state and in solution. The inclusion complexes with cyclodextrins do not involve any chemical bond formation. It is the hydrogen bonding and van der Waals forces between the host and guest which impart stability to the complexes. However, the successful complex formation does not ensure taste masking in certain cases. Cyclodextrin risperidone inclusion complex was fabricated in our laboratory using β- and HP- β-cyclodextrins and the complexation was confirmed using different characterization techniques like differential scanning calorimetry, x-ray diffraction and fourier transform infra red spectroscopy. However, the complex failed to mask the bitter taste of the drug. This was probably due to the low stability of the complex in the aqueous medium. Therefore, it may be concluded that in order to achieve sufficient taste masking ability a complex must have very high stability constant values.

Cyclodextrin complexation has been successfully employed for taste masking in case of carbetapentane citrate syrup (13), ibuprofen solution (14), gymnema sylvestre, a bitter and astringent tasting sweetener for diabetes control (15) and femoxetine, a new antidepressant (16). In another study, β- and γ-CDs were linked to chitosan through succinyl or maleyl bridges and this macromolecular adducts was evaluated for its taste masking ability with caffeine and bitter natural extracts (artichoke leaves, aloe and gentian) by a taste panel using serial caffeine concentrations as a reference scale. The β-CD-chitosan adduct showed the highest efficacy with statistically significant reduction in bitterness (17).

Taste masking by complexation of drugs with other excipients

The solubility and absorption of drugs can be modified by the formation of molecular complexes. Lowering drug solubility through molecular complexation can decrease the intensity of bitterness. The bitterness of caffeine was completely masked by the formation of a molecular complex of caffeine and gentisic acid in 1:1 and 1:2 molar ratios (18). The complex was prepared by rapid cooling of the hot aqueous solution of the mixture. The resulting microcrystalline powder precipitate was washed with water and dried under vacuum. In another study, the bitter taste of diphenhydramine (DPH), was masked using small molecular weight and carboxyl group containing polymers. Studies showed that DPH interacted with alpha-helical poly (glutamic acid) specifically to produce DPH/poly (glutamic acid) complexes, mostly spherical in shape with a diameter of around 1.0 μ (19).

Solid Dispersions

The formulation of drug particles into solid dispersion creates a physical barrier between the bitter drugs and the taste buds. In solid dispersion, one or more active ingredients are homogenously dispersed in an inert carrier or matrix in solid state. Carriers which may be used in solid dispersion systems include povidone, polyethylene glycols, cellulose derivatives, urea, sugars, polyethylene glycol, fatty acids, waxes, glycerides, etc. The various approaches for preparation of solid dispersion are described below.

***Melting method*:** In this method, the drug or drug mixture and a carrier (generally polyethylene glycol or lipids) are melted together by heating. The molten mixture is cooled and solidified rapidly in an ice bath with vigorous stirring. The final solid mass is crushed and pulverized. The method is not suitable for thermo-sensitive drugs. However, to reduce the duration of drug exposure to temperature, the drug may be added later to the molten carrier under vigorous stirring and cooled immediately.

***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. It must be taken care that the traces of solvent remaining in the formulation are well below the permissible limits in order to avoid toxicity.

***Melting-solvent method*:** In this method the drug in solution is incorporated into a molten mass of polyethylene glycol at a temperature below 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 (20).

Formation of salts and prodrugs

Chemical modification of the drug substance have also been tried so as to reduce its solubility in the saliva and thus reduce its sensitivity to the taste buds. The modifications are usually limited to salt formations as any other structural medication can have a drastic effect on the therapeutic value of the molecule. Aspirin was rendered tasteless by making magnesium salt of aspirin (21). The taste of chlorpheniramine was masked by formation of its maleate salt (22). It has been observed that addition of alkaline metal bicarbonate such as sodium bicarbonate masks the unpleasant taste of water soluble ibuprofen salts in aqueous solution (23). The bitter taste of caffeine can be masked by formulating it as a carbonated oral solid preparation using sodium bicarbonate, ascorbic acid, citric acid and tartaric acid (24).

Another approach is forming a prodrug which is a chemically inert drug precursor which readily liberates drug in biological system. Number of bitter tasting antibiotics and opoid analgesics have been converted into prodrugs and have been successfully taste masked. Palmitate salt of chloramphenicol, alkyl ester of clindamycin, lincomycin and erythromycin are few examples (25-28).

Use of amino acids, protein hydrolysates and taste masking flavor

Amino acids or their salts when used in combination with bitter drugs have the ability to significantly reduce their bitter taste. The amino acids commonly used are taurine, sarcosine, alanine, glycine and glutamic acid. Anticholesterolemic saponin containing foods, beverages and pharmaceuticals are supplemented with amino acids (such as glycine and alanine) and flavors to control their bitterness (29). Protein like composition, useful for liver disorders, severe burns, trauma, etc. is mixed with branched amino acids which convert the unpleasant tasting proteins to tasteless and odorless products (30). Apart from the above excipients use of readymade taste masking flavors in the formulations alone or in combination with other taste masking excipients/approaches not only mask the taste of drug but also provide pleasant taste and mouth feel to the formulation. The taste of ampicillin improved markedly by preparing its granules with glycine and mixing them with addtional quantity of glycine, sweeteners, flavors and finally compressing them into tablets (31).

Taste-masking by rheological modifications

Viscosity of a formulation plays an important role in the process of taste masking of bitter drugs. Increase in viscosity of formulations due to the addition of thickening agents like gums or carbohydrates, can lower the diffusion rate of the drug molecules into the taste buds. Thickening agents such as polyethylene glycol and sodium carboxymethylcellulose are generally used in the development of taste-masked liquid formulation. The addition of these agents provides additional stability of the liquid formulations especially in case of suspensions. The use of thickening agents should not hamper the pourability of the formulation. Bitter taste of acetaminophen suspension was masked by addition of xanthan gum (0.1–0.2 %) and microcrystalline cellulose (0.6–1%) as viscosity modifier (32). The syrup containing phenobarbital or acetaminophen was masked by polyethylene glycol or polypropylene glycol with polyvinyl pyrollidone, gum arabic or gelatin (33). Gelatin and flavoring materials (chocolate flavor) masked the bitter taste of tannic acid by viscosity modification (34). Other commercially available pharmaceutical compounds like pseudoephedrine HCl, dextromethorphan and ibuprofen have also been successfully taste masked by this technique (35).

Conclusion:

Although there are number of taste masking techniques for effective taste-masking of the objectionable taste of drugs but there application requires skill so that it does not affect the bioavailability of drug. With application of these techniques and proper evaluation of taste masking effect one can improve patient compliance of the products to a larger extent. Moreover, the development of taste masking methodology requires great technical skill and need massive experimentation.

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