ISSN : 2320 4850

BI MONTHLY

Asian Journal of Pharmaceutical Research And Development

(An International Peer Reviewed Journal of Pharmaceutical Research and Development)

AJPRD

Volume - 02 Issue - 03 MAY-JUN 2014

website: www.ajprd.com
editor@ajprd.com

Asian Journal of Pharmaceutical Research and Development
(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)
www.ajprd.com
ISSN 2320-4850

Review Article

TASTE MASKING: A NOVEL TECHNIQUE FOR ORAL DRUG DELIVERY SYSTEM

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Received: June 2014 ***Revised and Accepted: July2014***

ABSTRACT

Oral administration of pharmaceuticals is one of the most popular methods of drug delivery. Many orally administered drugs elicit bitter taste. Palatability is an extremely important factor in ensuring the likelihood that the recipients will intake the pharmaceuticals. A constant problem is in treatment of patient is their inability or unwillingness to swallow solid dosage forming such as tablets especially in children and the elderly. These dosage forms permit perceptible exposure of active drug ingredient to the taste bud. Accordingly, masking of unpleasant taste characteristics of drug is an important factor in formulation of these agents. "The worse the taste of the medication, the better the cure" was once the prevailing attitude. Today a change in patient attitude and development of taste masking technique has reversed this opinion. Patients now expect and demand formulations that are pleasantly, or at least tolerably, flavored. This article reviews the earlier methodologies and approaches of taste masking techniques of bitterness reduction.

Keywords: *Taste masking, Taste bud, Bitter, Patient compliance, Drug product, Dosage form*

INTRODUCTION

Drug delivery systems intended to disintegrate within the buccal cavity such as mouth dissolving tablets, orally disintegrating tablets and chewable tablets are very popular due to the patient compliance. 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 required to fulfil certain organoleptic properties among which taste is a major property. Other types of formulations that 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.

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These are two approaches which are commonly used to overcome bad taste of the drug [1]. 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.

TASTE SENSATION

Taste is an important parameter in administering drugs orally. Undesirable taste is one of the important formulation problems that are encountered with many drugs. Administration of bitter drugs orally with acceptable level of palatability is a key issue for health care providers.

Taste is the ability to detect the flavor of substances like food, drugs etc. Taste is now became an important factor governing the patient compliance. It gained importance as the most of the drugs are administered through oral route. Administration of unpalatable drugs is hampered by their unpleasant taste

particularly in case of pediatric and geriatrics [2].

Taste is the ability to respond to dissolved molecules and ions- "gatekeeper to the body". Human detects taste with taste receptor cells that are clustered in to onion-shaped organs called taste buds. Each taste bud has a pore that opens out to surface of the tongue enabling molecules and ions taken into the mouth to reach the receptor cells inside.

Human have around 10,000 taste buds which appear in fetus at about three months. A single taste bud contains 50-100 taste cells. Each taste cells receptors on its apical surface. These are Trans membrane proteins which bind to the molecules and ions that give rise to the four primary taste sensations namely - salty, sour, sweet and bitter.

There is often correlation between the chemical structure of a compound and its taste. Low molecular weight salts tend to taste salty where as high molecular weight salts tend toward bitterness. Nitrogen containing compounds, such as alkaloids, tend to be quite bitter. Organic compounds containing hydroxyl groups tend to become increasingly sweet as number of OH group increase. Receptor mechanism involves initial depolarization at apical receptor site, which causes local action potential in receptor cell. This in turn causes synaptic activation of the primary sensory neuron. Four basic tastes are confirmed to specific regions of tongue. 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 a taste. The following table 1 gives the threshold concentration of four primary taste sensations. It can be seen that tongue is 10,000 times more sensitive to the bitterness of quinine than to sweetness of sugar. Saccharine, on this scale would rate about 0.001%. Pharmaceutical companies can save themselves much grief by addressing the taste factor early in the product development. In so doing, they can get their medications to market more quickly, ensure patient compliance, gain market leadership and reap generous economic rewards. They can also stay in compliance with FDA's final rule, which went into effect December 2000 [3].

Types and Mechanism of Taste

Taste is one of the traditional five senses and is the ability to detect the flavor of substances such as food, certain minerals, and poisons, etc. It determines the selection of food, its palatability and stimulation of reflexes for secretion of saliva, gastric juices and pancreatic juices. The sensation of taste can be categorized into [4, 5]:

Sweet (sugars, glycerol)
Salty (sodium)
Sour (acidic substances)
Bitter (quinine, nicotine)
Umami

Salt taste

Salt is sodium chloride (Na^+ Cl^-). Na^+ ions enter the receptor cells via Na-channels. These are amiloride -sensitive Na+ channel (as distinguished from TTX-sensitive Na+ channels of nerve and muscle). The entry of Na^+ causes a depolarization, Ca^{2+} enters through voltage sensitive Ca^{2+} channels, and transmitter release occurs and results in increased firing in the primary afferent nerve.

Sour taste

Sour taste is acid and acid is proton (H^+). There is exciting new evidence that there is an acid-sensing channel - the PKD2L1 channel1.This channel is a member of the transient receptor potential channel (TRP) family and is a non-selective cation channel. The activity of PKD2L1 is gated by pH (H^+ ion concentration). This new discovery displaces the previous ideas that H^+ ions block K^+ channels causing a depolarization, or that H^+ ions enter the cell through ENaC channels. These mechanisms may exist but do not lead directly to sour perception.

Sweet taste

There are receptors T1R2 + T1R3) in the apical membrane that bind glucose (sucrose - a combination of glucose and fructose – and

other carbohydrates). Binding to the receptor activates a G-protein which in turn activates phospholipase C (PLC-ß2). PLC generates IP3 and diacyl glycerol (DAG). These intracellular messengers, directly or indirectly, activate the TRPM5 channel and depolarization occurs. Ca^{2+} enters the cell through depolarization-activated Ca^{2+} channels; transmitter is released increasing firing in the primary afferent nerve.

Bitter taste

Bitter substances bind to the T2R receptors activating the G-protein and causing activation of PLC. The second messengers DAG and IP3 are produced (by hydrolysis of phosphatidylinositol-4, 5-bisphosphate) activating TRPM5 and mediating release of Ca^{2+} from internal stores. The elevated Ca^{2+} causes transmitter release and this increases the firing of the primary afferent nerve.

Umami taste

Umami is the taste of certain amino acids (e.g. glutamate, aspartate and related compounds). It was first identified by Kikunae Ikeda at the Imperial University of Tokyo in 1909. It was originally shown that the metabotropic glutamate receptor (mGluR4) mediated umami taste. Binding to the receptor activates a G-protein and this elevates intracellular Ca^{2+}. More recently it has been found that the T1R1 + T1R3 receptors mediate umami taste. Humans receive tastes through sensory organs, taste buds (also known as gustatory calculi) concentrated on the upper surface of the tongue.

Taste buds

Taste buds are the structures present primarily on the surface of tongue which contains receptors that mediate the sense of taste.

Distribution

Taste buds are also present on palate, pharynx, epiglottis and larynx. Tongue consists of numerous structures called papillae. There exists different type of papillae, of which fungi form papillae contain single taste bud on the tip and circum vallate papillae contains several taste buds. However, filiform papillae do not contain taste buds even their number is more [6]. Different types of tastes have different threshold concentration based on the distribution of taste buds on surface of the tongue, enlisted in Table 1.

Table I: Specific area of tongue and threshold concentration for primary taste sensations

Taste	Area of Tongue	Threshold concentration (%)
Sweet	Tip of tounge	0.5
Salt	Tip and side of tounge	0.25
Sour	Side of tounge	0.007
Bitter	Back of tounge	0.00005

Structure

Taste bud is oval in shape and opens into epithelial surface through a small opening called taste pore (Figure 1). Microvillus protrudes from the taste pore arising from the individual taste cells. Each taste bud has 50-100 receptors and support cells. Based on the electron microscopy, receptors are classified into basal, dark, intermediate and light.

The receptors are connected through synapse (ATP releasing) to sensory neuron, leading back to the brain. The sensation of taste thus resides in the brain. However, a single sensory neuron can be connected to several taste cells [4, 5].

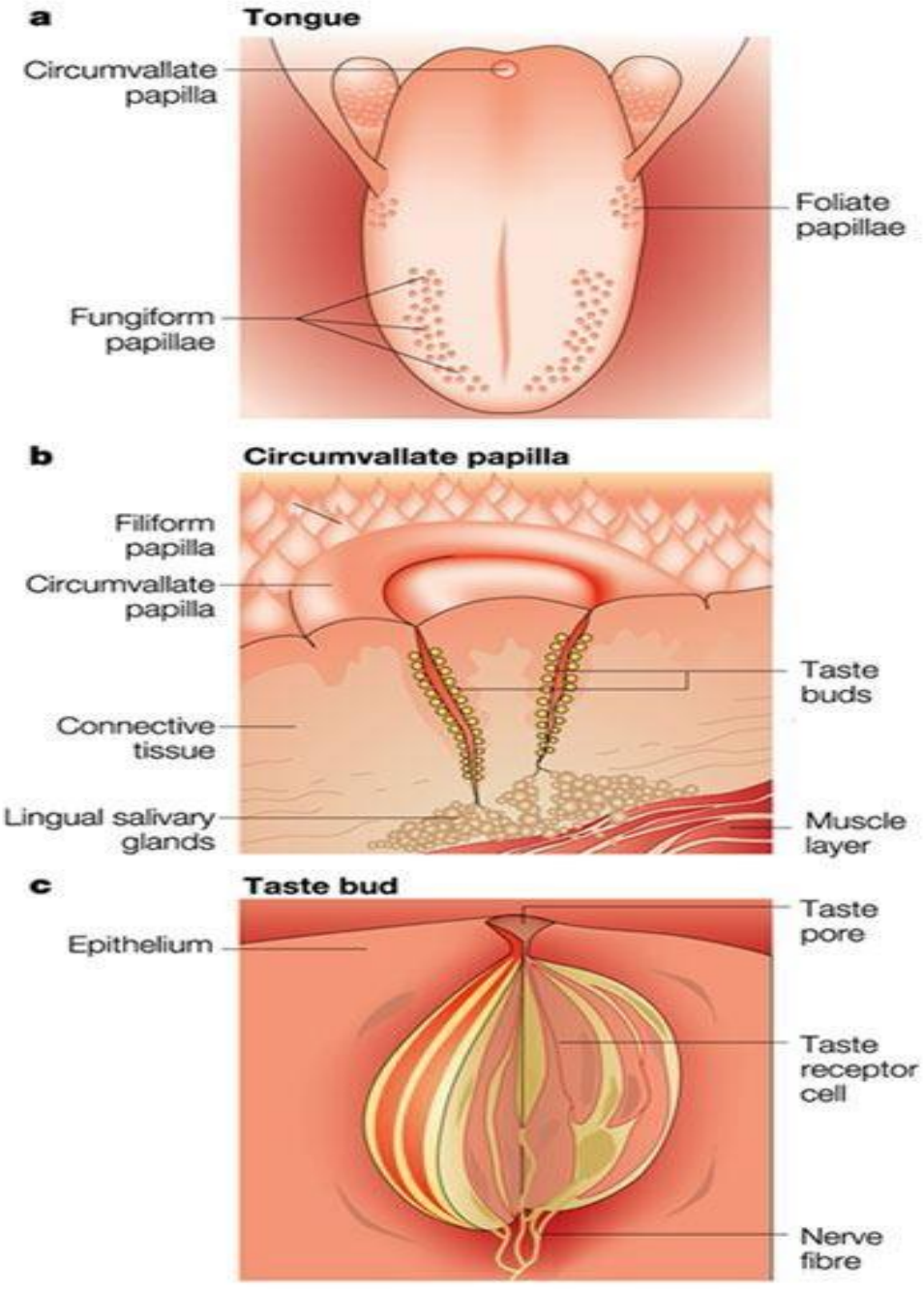

Figure. 1: Structure of taste bud

FACTORS THAT ARE TAKEN INTO CONSIDERATION DURING THE TASTE-MASKING FORMULATION INCLUDE [7 - 12].

Extent of the bitter taste of the API
Required dose load
Drug particulate shape and size distribution
Drug solubility and ionic characteristics
Required disintegration and dissolution rate of the finished product
Desired bioavailability
Desired release profile
Required dosage form

So major taste masking efforts are required before bitter drugs are acceptable for market trials. Major taste masking technologies are based on the reduction of solubility of the drug in the saliva so the drug concentration in saliva

will remain below taste threshold value. The desire for improved palatability of formulations has prompted the development of various new technologies for taste abatement. Many of these technologies have been successfully commercialized. But, the ideal solution of taste masking would be the discovery of universal inhibitor of bitter taste of all drugs.

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 and saltiness. Two comprehensive reviews to control bitter taste have already been reported along with thoughts on the discovery of a universal bitterness inhibitor [13 - 14].

Various techniques reported in the literature are as follows [7 – 8, 10 -12, 15].

Addition of flavors and sweeteners

Lipophilic Vehicles like lipids and lecithin's

Coating

Salt Preparation of bitter drugs

Inclusion complexes

Prodrug approach

Effervescent agent Granulation

Microencapsulation

Adsorption

Prodrug approach

Effervescent agent Bitterness inhibitors

Granulation

Taste suppressants and potentiators

Multiple emulsions

Solid dispersion system

Gel formation

Rheological modification

Flavors and sweeteners

This technique is simplest approach for taste masking. But this approach is not very successful for highly bitter drugs. Artificial sweeteners and flavors are generally being used along with other taste-masking techniques to improve the efficiency of these techniques [16 - 17]. Eucalyptus oil is a major constituent of many mouth washes and cough drop formulations which is a bitter tasting substance. Its bitter taste can be masked by agent including fenchone, borneol or isoborneol [18].

Cooling effect of certain flavoring agent aids in reducing perception of bitterness. The physiology involved is merely to numb taste buds, either rapidly or over a period of time, so that the cooling effect actually builds up after ingestion. The brain perceives the coolness even though physically the temperature of the product has not changed [19]. Some generalization concerning the selection of flavors to mask specific types of taste has been suggested [20].

A combination of flavoring agents is usually employed. Flavor adjuvant like menthol and chloroform are considered as a desensitizing agents because addition to their own odor and flavor they also have mild anesthetic effect on taste receptors. Aspirin medicated floss contains sodium phenolate as an anaesthetizing agent in addition to chocolate flavor to mask the bitter taste of aspirin [21].

A survey of the taste preferences of human race, as a whole, indicates that sweet taste is very agreeable to our species. Hence for controlling the taste qualities effort are directed to make the preparations sweet to different degrees. Sweeteners are commonly used for this purpose. **Table: 2** [22] presents a compilation of the most common artificial and natural sweeteners used in pharmaceutical products, their relative sweetness levels, and pertinent comments. Aspartame is used as prominent sweetener in providing bitterness reduction. A very small concentration (0.8%) is effective in reducing bitterness of 25% acetaminophen. Cyclamates have been banned by the USFDA since 1970 due to its carcinogenic effect. The neohesperidine dihydrochalone is an artificial bitterness suppressor and flavor modifier. It is an open chain analogue of neohesperidine, a bitter flavanone that occurs in Seville oranges (citrus aurantium). Taste masking properties of the neohesperidine dihydrochalone have been reviewed by Cano et al. It is a bitterness suppressor and flavor modifier that also elicits a very intense lingering sweet taste. Due to its

lingering sweet taste the taste of bitter substance appears later in time and taste could be masked.

Active ingredient is significantly objectionable in taste then flavors alone are unable to yield a completely satisfactory product. Major taste masking efforts are required before they are acceptable for market trials. But this approach can always play a significant supportive role to other taste masking approach.

Table II: List of commonly used sweeteners and their relative sweetness

Sweetening Agents	Relative sweeteners*	Significance
Aspartame	200	Less stable in solution
Acesulfame potassium	137-200	Bitter in higher concentration
Cyclamate	40	Banned
Glycerrhizin	50	Moderately expensive
Lactose	0.16	High amount is required
Manitol	0.60	Negative heat of solution
Saccharin	450	Unpleasant after taste
Sucrose	1	Most commonly used
Sucralose	600	Synergestic sweetening effect

Lipophilic Vehicles like lipids and lecithin's

Oils, surfactants, poly alcohols, and lipids effectively increase the viscosity in the mouth and coat the taste buds, and therefore they are potential taste masking agents. Guaifenesin has improved taste when mixed with carnauba wax and magnesium aluminum silicate and then melt-granulated. The taste of cimetidine can be improved by granulating it with glycerol mono stearate.

Hydrophilic polymer coating

This is the simplest and most feasible option to achieve taste masking. The coating acts as a physical barrier to the drug particles, thereby minimizing interaction between the drug and taste buds. Coating of chewable tablets provides excellent taste masking while still providing acceptable bioavailability. A canalized technique, i.e., micro emulsion technology, has been used for taste masking of powders, chewable tablets, and liquid suspensions.

Salt Preparation of bitter drugs

Adding alkaline metal bicarbonate such as sodium bicarbonate masks the unpleasant taste of water soluble ibuprofen salts in aqueous solution. The bitter taste of caffeine may be masked by formulating it as a carbonated oral solid preparation using sodium bicarbonate, ascorbic acid, citric acid, and tartaric acid. Magnesium aspirin tablets are rendered tasteless by preparing magnesium salts of aspirin.

Formation of inclusion complexes

Inclusion complex is a 'host-guest' relationship in which the host is complexing agent and guest is the active moiety. The complexing agent is capable of masking bitter taste either by decreasing its oral solubility or decreasing the availability of drug to taste buds. Vanderwaal forces are mainly involved in inclusion complexes [6 – 15, 23 - 25]. β - Cyclodextrin is widely used complexing for

taste masking of drugs due to its sweet taste and is non toxic in nature

Prodrug approach

Prodrugs are therapeutic agents that are initially inactive but on biotransformation liberate active metabolite by which the therapeutic efficacy is obtained. Molecular geometry of the substrate is important for the taste receptor adsorption reaction i.e., mechanism of taste. Hence if any alteration is done in molecular geometry, it lowers the adsorption rate constant. Thus taste masking can be achieved through prodrug approach. Other advantages of prodrugs include change in aqueous solubility, increase lipophilicity, improved absorption, less side effects and change in membrane permeability etc. [12, 15 15, 26]. **Table 3** gives a list of active moieties and their prodrug approaches done in recent years.

Table III: Literature report on taste masking by prodrug approach

Drug	Category	Modification done
Chloramphenicol	Broad spectrum antibiotic	Palmitate or phosphate ester
Clindamycin	Lincosamide antibiotic	Alkyl ester
Erythromycin	Macrolide antibiotic	Alkyl ester
Lincomycin	Lincosamide antibiotic	Phosphate or alkyl ester5
Tetracycline	Broad spectrum antibiotic	3,4, - trimethoxy benzoate salts
Triamcinalone	Treatment of ulcerative colitis	Diacetate ester

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. A chewing gum composition of bitter medicament(s) was formulated to supply the medicament(s) to the oral cavity for local application or for buccal absorption [27, 28].

Microencapsulation

Microencapsulation is a process in which the active moiety (solid or liquid droplets) is coated with a polymeric material or film. Types of microencapsulation include [7, 8, 12, and 15].

- Air suspension coating
- Coacervation phase separation
- Spray drying
- Spray congealing
- Solvent evaporation
- Pan coating
- Interfacial polymerization etc.

From these processes, first four are mostly used techniques for achieving taste masking. Microencapsulation by coacervation phase separation consists of three steps carried out under Continuous agitation, such as: formation of three immiscible phases, deposition of coating and Rigidization of coating.

Polymers and their selection

Selection of coating polymer is an important factor to be considered for taste masking by coating.

Ideal characteristics of a coating polymer

Should not allow the release of drug in oral cavity, but should allow the release of the drug at the expected site (intestine or stomach).
Should be insoluble in salivary pH (6.8) but Should be soluble in gastric pH (1.2)
Choosing one of the polymers is not a simple selection. Before making the decision on

coating material, the following factors of drug are to be considered [29, 30].

Particle size
Flow properties
Moisture sensitivity
Long term stability
Effect of temperature on processing
Form of Drug delivery etc.

Once the type of coating and polymer is decided, then the level of coating has to be optimized. Thick coating may cause problems both in terms of size and cost. However, by coordinating the right type of coating material it is possible to mask the bitter taste of the drug completely while at the same time not affecting the intended drug release. **Table 4** gives a literature report on various coating materials used for taste masking the drugs.

Table IV: Literature report on taste masking by microencapsulation

Drug	Category	Dosage form	Coating material used
Acetaminophen	Anti pyretic	Dispersible tablet	Cross carmellose
Caffeine / Cimetidine	Diuretic / Anti histamine	Chewable tablet	Eudragit RL 30D, RS 30D
Ciprofloxacine	Fluoroquinolone antibiotic	Oily suspension	Eudragit NE 30D/ RL 30D, HPMC
Levofloxacine	Fluoroquinolone antibiotic	Suspension	Eudragit E 100, Cellulose acetate
Sildenafil citrate	Vaso dilator		Eudragit NE 30D, E 100
Chlorpheneramine maleate	Anti histamine	Mouth melt tablet	Ethyl cellulose
Dextromethorphan hydrobromide	Anti tissue		PVP-K30
Acetaminophen	Antipyreyic	Chewable tablet	Eudragit E 100, Cellulose acetate
Theophylline	Antipyretic	Dry suspension	Eudragit NE 30D, Guargum
Ampicillin trihydrate	Penicillins	Powders	Sodium CMC
Nizatidine	Anti histamine	Sprnkels	Eudragit E 100
Roxithromycin	Macrolides	Suspension	Eudragit RS 100/RL 100
Clarithromycin	Macrolides	Powders	Glyceryl monosterate, Eudragit E 100
Chloroquine diphosphate	Anti malerial	Powders	Eudragit RS 100
Metronidazole	Anti amoebic	Dry suspension	Eudragit E

Granulation

Taste masking of a bitter taste drug can be masked by granulation process. Granulation is major and a common process in tablet production. In this approach, saliva insoluble polymers are used as binding agents in the tablet preparation. As these polymers are insoluble in saliva, thus the bitter taste of the drug can be masked [8 – 10]. The taste masked granules can also be formulated as chewable tablet and rapidly disintegrating tablets. Table

no.13 gives the literature report on the list of drugs whose taste is masked by granulation techniques by using saliva insoluble polymers. Taste masked granules of bitter tasting drug pirenzepine and oxybutynin have been prepared by the extrusion using amino alkyl methacrylate copolymer. (EudragitE-100)[31, 32].

Adsorption

Adsorbate of bitter tasting drug can be considered as less saliva soluble version of that drug. In this technique, adsorbates of the bitter drugs are prepared by adsorption process. This process involves the adsorption of the drug solution using insoluble materials like silica gel, bentonite, veegum etc. The adsorbate (resultant powder) is dried and used for the formulation of final dosage forms [12, 33].

Taste suppressants and potentiators

Most of Linguagen's bitter blockers (adenosine mono phosphate) compete with bitter substances to bind with GPCR sites. In general, hydrophobic nature of these bitter substances has good binding affinity to the receptor sites. Lipoproteins are universal bitter taste blockers. Neohesperidine phospholipids have bitter taste suppression characteristics by chemically interacting with the taste receptors. Cooling and warming agents suppress unpleasant taste of medicament by subjecting taste receptors to extreme sensations to overcome/ overpower the bitter taste so as to confuse the brain. Eucalyptol (Cooling agent) and Methyl salicylate (Warming agent) mixture was used for suppression of the bitter taste of Thymol [5, 7, 8].

Potentiators increase the perception of the taste of sweeteners and mask the unpleasant taste. Various potentiators include thaumatine; neohesperidine dihydro chalcone (NHDC) and glycyrrhizin increase the perception of sodium or calcium saccharinates, saccharin, acesulfame, cyclamates etc. Thaumatine along with sugar alcohols to achieve taste masking of bromhexine [7, 10].

Liposomes and multiple emulsions

Liposomes are carrier molecules comprising several layers of lipids, in which the bitter drug is entrapped within the lipid molecule. Oils, surfactants, polyalcohols and lipids effectively increase the viscosity in the mouth due to which the time of contact between the bitter drug and taste receptors is decreases, thus improving the overall taste masking efficiency.

Inhibition of bitterness of drugs by phospholipids such as phosphatidic acid, phosphatidylinositol, soya lecithin etc has been reported. The bitterness of chloroquine phosphate in HEPES buffer (pH 7.2) is masked by incorporating into a liposomal formulation prepared with egg phosphatidyl choline [7, 8]. Multiple emulsions are also a good approach for taste masking of bitter drugs. This is achieved by dissolving the drug moiety in the inner aqueous phase of w/o/w emulsion with good self life stability. The o/w/o emulsion is a type of multiple emulsions in which water globules themselves containing dispersed oil globules, conversely w/o/w emulsions are those in which internal and external aqueous phases are separated by the oil. Both types of multiple emulsions are prepared for Chloroquine sulphate and reported to be partially effective in masking the bitterness of the drug. Examples of drug listed in table no: 15 indicates the use of liposomes and multiple emulsions technique in taste masking [7, 8].

Solid dispersion system

Solid dispersion has been defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting (fusion) solvent or melting solvent method. Carriers used in solid dispersion system include povidone, polyethylene glycols of various molecular weights, hydroxy propyl methyl cellulose, urea and mannitol and ethyl cellulose.Various approaches for preparation of solid dispersion are described below -

Melting method

In this method, the drug or drug mixture and a carrier are melted together by heating. The melted mixture is cooled & solidified rapidly in an ice bath with vigorous stirring. The final solid mass is crushed & pulverized.

Solvent method

In this method, the active drug and carrier are dissolved in a common solvent, followed by solvent evaporation and recovery of the solid dispersion.

Melting solvent method

In this method drug in solutions is incorporated into molten mass of polyethylene glycol at a temperature 70˚C without removing the solvent [23].

Molecular complexes of drug with other chemicals

The solubility and adsorption of drug can be modified by formation of molecular complexes. Consequently lowering drug solubility through molecular complex formation can decrease the intensity of bitterness of drug, Higuchi and pitman, reported that caffeine forms complexes with organic acids that are less soluble than xanthenes and as such can be used to decrease the bitter taste of caffeine [23].

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 substance 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 [34, 35]. Bitter substances are commonly hydrophobic in nature hence lipoprotein (PA-LG) composed of phophatidic acid and β-lacto globulin can mask the target sites for bitter substances on the taste receptor membrane without affecting responses to salts, acids, sugars or sweet amino acids.

Bitter taste of brucine, berberine, chloride, caffeine, denatonium benzoate, glycyl L-leucine, L-phenylalanine, naringin, propranolol hydrochloride, quinine hydrochloride, strychnine nitrate and theophylline [36-38] have been suppressed by lipoprotein. Selective inhibition of bitter taste of various drugs by phospholipids such as phosphatidic acid, phosphatidylinositol and soya lecithin have been reported [39]. Bitter taste of polymixin B sulfate and trimethoprim-sulfamethoxazole has been masked by BMI 60 obtained by fractionating soya lecithin [40].

The w/o/w or o/w/o type multiple emulsions are vesicular systems in which active ingredient can be entrapped in internal phase. The entrapped substances can be transferred from internal phase to external phase through the ‘membrane phase’. This phase controls the release of drug from system. This system could be used for controlled-release delivery of pharmaceuticals. If the system is stable enough for a reasonable shelf life, the formulation could also mask the taste of drug [41]. Both w/o/w or o/w/o multiple emulsions of chloroquine phosphate have been prepared and reported to be partially effective in masking the bitter taste of drug [42].

Gel Formation

Water insoluble gelation on the surface of tablet containing bitter drug can be used for taste masking. Sodium alginate has the ability to cause water insoluble gelation in presence of bivalent metal ions. Tablet of amiprolose hydrochloride have been taste masked by applying an undercoat of sodium alginate and overcoat of calcium gluconate. In presence of saliva, sodium alginate react with bivalent calcium and form water insoluble gel and thus taste masking achieved [43].

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. Acetaminophen suspension can be formulated with xanthan gum (0.1-0.2%) and microcrystalline cellulose (0.6-1%) to reduce bitter taste [44].The antidepressant drug mirtazapine is formulated as an aqueous suspension using methonine (stabilizer) and maltitol (thickening agent). Maltitol is stable in the acidic pH range of 2 to 3 and besides masking the unpleasant taste of the drug, it also inhibit its undesirable local anesthetic effect [45].

EVALUATION TECHNIQUES

Sensory evaluation

Taste, to think of, is a very subjective perception. Depending on individuals, the perceived taste may vary to different degrees. If we have well controlled experimental set up, it is possible to accurately and reproducibly measure taste thresholds. To quantitatively evaluate taste sensation, following methods have been reported in literature

- Panel testing (human subjects)
- Measurement of frog taste nerve responses.
- Multichannel taste sensor/ magic tongue
- Spectrophotometric evaluation/ D30's value

Panel Testing

The panel testing is a psychophysical rating of the gustatory stimuli. In this method, a group of about 5-10 human volunteers is trained for taste evaluation by using reference solutions ranging in taste from tasteless to very bitter. Numerical values are then assigned to these levels of bitterness (e.g. 0-5). Subsequently, test solution is tasted and rated on the same scale to assess its bitterness.

Literature reports panel testing in invariably all the taste-masked frogs being evaluated. The ease of the method combined with the accuracy of human perception of taste against any other gustatory evaluation technique makes panel testing the most commonly used technique [46].

Measurement of Frog Taste Nerve Responses

In this method, adult bull frogs are anaesthetized intraperitoneally and the gloss pharyngeal nerve is then located and dissected from the surrounding tissue and cut proximally. An ac-amplifier and an electronic integrator are used to respectively amplify and integrate the nerve impulses. The peak height of the integrated response is then taken as the magnitude of response. Quinine sulphate formulations, taste masked by PA-LG (phosphatidic acid-lacto globulin) combination has been reported to be evaluated by this technique [38].

Multichannel Taste Sensor / Magic tongue

This is an automated taste sensing device to detect the magnitude of bitterness of a drug substance. The device has a transducer which is composed of several kinds of lipid/polymer membranes with different characteristics that can detect taste in 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 [47].

Recently, the technique has been applied, for the quantitative evaluation of the bitterness of some commercially available medicines. Quinine hydrochloride was taken as the standard for bitterness. Basic drug with amino groups in the molecule such as quinine, show a comparatively good correlation between the relative response electric potential (mV) of channels 1 or 2 of the taste sensor, which contain negatively charged membranes, and the bitterness as determined by human gustatory sensations tests.

Secondly, for anionic drugs, such as diclofenac sodium or salicylic acid, the positively charged membrane in channel 5 or 6 seemed to the useful even through; they are being sour rather than bitter. For drugs with both an amino (cationic) groups and a carboxylic acid (anionic) group in the molecule, such as theophylline, caffeine and metronidazole, the electric potential (mV) of channel 1 or 2 did not increase, even though bitterness was observed in human gustatory

sensation test. Therefore, different types of membrane component will be needed for a complete evaluation of the bitterness of medicines [48].

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*. This technique has been applied to evaluate the taste masked granules of sparfloxacin, with threshold concentration being 100µg/ml [49].

RECENT TRENDS [50 - 52].

AdvaTab ODT Technology

Advatab ODT Technology is developed by APTALIS Pharmaceutical technologies. Various advantages offered by this technology include high physical stability, stability during package and transport, pleasant taste (with Microcap technology) and good patient compliance.

Microcap ODT Technology

Microcap ODT technology is developed by APTALIS Pharmaceutical technologies. This technology uses coating method for taste masking. The polymeric membrane eliminates the unpleasant taste and or odor. Offer advantages like precise taste masking, good release profiles and patient compliance.

Liquitard ODT Technology

This sophisticated Liquitard technology is developed by APTALIS Pharmaceutical technologies with an aim to provide an effective, convenient, ready-to-use, taste-masked powder formulation in single dose sachets that can be administered as a suspension or sprinkle on easy to swallow foods. This is developed with a wide variety of flavors and is compatible with customized release profiles.

Formulplex and Formulcoat

Pierre Fabre developed a new taste masking technologies in which, coating of micro or nanosized particles at room temperature with non organic solvent.

KLEPTOSE® Linecaps

Roquette offers a new taste-masking technology: KLEPTOSE® Linecaps, uses a pea maltodextrin for masking the bitter taste of drugs by decreasing the overall amount of drug particles exposed to the taste buds.

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 affects one can improve patient compliance of the product to a larger extent. Taste masking of bitter drugs is a big challenge to scientist. However we have made an attempt to describe various methods, techniques suitable for taste masking of obnoxious drugs. These techniques mentioned in this review can be used for bench scale and pilot scale also. In addition to the existing patented taste masking technologies, several new technologies for effective taste masking are also mentioned in this review. With application of these techniques one can improve product preference to a large extent. In addition to oral drug delivery, the taste masked drug delivery research is gaining importance for the quality of thetreatment provided to patients, especially children and old. As evidenced by number of patients and technology developments, an attempt of ideal taste masking is widely accepted in the development of palatable dosage forms having good patient compliance without interfering the drug release.

ACKNOWLEDGEMENT

The authors acknowledge the Sinhgad College of Pharmacy (S. No. 44/1), Pune - 411041, India for providing financial assistance. The authors also want to thank the library of the college for providing e-resources available. I am very thankful to College for supporting me at each and every step of my work.

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