ISSN: 0975-766X
CODEN: IJPTFI
Review Article

Available through Online
www.ijptonline.com

TASTE MASKING TECHNIQUES FOR BITTER DRUGS-AN OVERVIEW

Munira Momin*, Sudha Rathod, Swapan Kar
Dept. of Pharmaceutics, Oriental College of Pharmacy, Sector-2, Plot 3,4,5, Near sanpada railway station Sanapada (W), Navi Mumbai 400705.
Email: momin_munira@hotmail.com

Received on 10-06-2012 *Accepted on 22-05-2012*

Abstract

Taste is mainly a function of taste buds in the mouth. In the formulation for pediatric & geriatric, bed ridden & non-cooperative patients the main challenge to the compounding pharmacist is to mask the taste of obnoxious and bitter drugs, result is patient not receiving the optimal therapeutic value of their medication. Taste masking is the main factor in the development of the dosage form. It opens the doors for new inventions and patents. Many techniques have been developed which not only improve the taste of molecule but also the formulation and performance of the molecule. The main objective of present review is to explore different method, technologies and evaluations to mask the obnoxious taste of drugs, so that patients can use these drugs without hesitation of taste.

Key words: Bitter taste, taste buds, taste masking techniques.

Introduction

In earlier days it was believed that the drugs having bitter taste are more efficient as well as more curable. This concept has been reversed with development of numerous formulation techniques. In recent era oral administration of bitter drugs with an acceptable degree of palatability becomes key issue for the health care providers, especially for pediatric and geriatric patients. Palatability is the combination of sensory perceptions including taste and smell and to a lesser extent texture, appearance and temperature of the products. Taste transduction involves the interaction of molecule with taste receptor cells, which reside in specific structures known, as TASTE BUDS. The function of taste buds is to relay information about the taste of the molecule to the central nervous system. Each taste type affects the receptor cells through distinct mechanisms. The transduction of most bitter and sweet compounds is mediated by G protein gustducin

while for salty and sour, is done by ion channels. Dissociation of gustducin into alpha and beta subunit decreases cAMP level and activate phospholipase C, which generates second messenger IP3 and DAG. This complex cascade of bio chemical events results in taste cells sending a signal to the brain that is interpreted as bitter and unpleasant. Thus preventing interaction between active molecule and taste bud could mask bitter taste.

Numbers of therapeutically active herbal molecules are having bitter taste. The unpleasant and unacceptable taste can be modified using below mentioned suitable techniques. Since last two decades large numbers of industrially viable techniques, are very well explored for the taste masking of bitter drugs. The present article gives an overview of past and current scenario of taste masking techniques. (1,2)

The physiology of taste buds

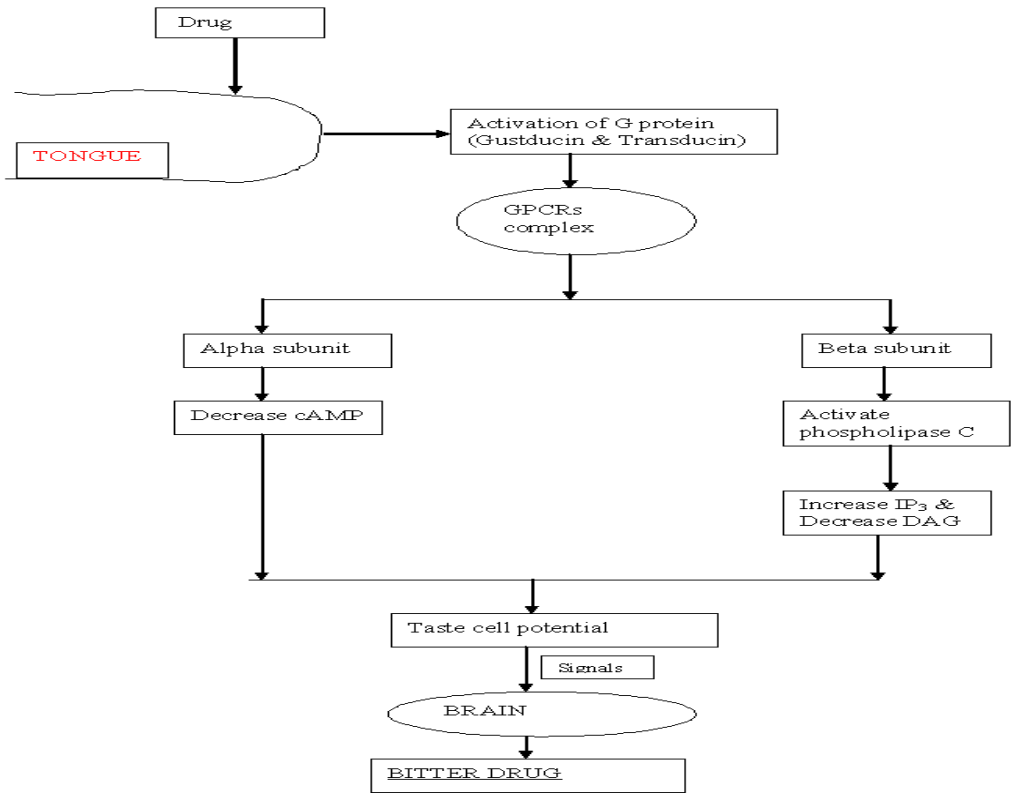
The basic understanding of physiology and functioning of taste buds is very essential in order to design any strategy for taste masking of formulations.

Taste buds are onion-shaped structures containing between 50 to 100 taste cells. The active ingredients taken orally in liquid/ uncoated/ mouth dissolve dosage forms first come in contact with oral cavity where they get dissolved by the saliva and enter via the taste pore. There they either interact with surface proteins known as taste receptors or with pore-like proteins called ion channels. These interactions cause electrical changes within the taste cells that trigger them to send chemical signals that translate into neurotransmission to the brain. Salt and sour responses are of the ion channel type of responses, while sweet and bitter are surface protein responses. The electrical responses that send the signal to the brain are a result of a varying concentration of charged atoms or ions within the taste cell. These cells normally have a net negative charge. Tastants alter this state by using varying means to increase the concentration of positive ions within the taste cell. This depolarization causes the taste cells to release neurotransmitters, prompting neurons connected to the taste cells to relay electrical messages to the brain.

In the case of bitter taste, such as quinine, stimuli act by binding to G-protein coupled receptors on the surface of the taste cell. This then prompts the protein subunits of alpha, beta, and gamma to split and activate a nearby enzyme. This enzyme then converts a precursor within the cell into a “second messenger.” The second messenger causes the release of calcium ions (Ca++) from the endoplasmic reticulum of the taste cell. The resulting build-up of calcium ions within the

cell leads to depolarization and neurotransmitter release. The signal now sent to the brain is interpreted as a bitter taste. Based upon the recent theory that taste cells can interpret and process all the different stimuli, a method of diminishing the overall response to one stimulus would be to introduce a second stimulus. This is based upon the assumption that differences among responses to stimuli are not so much a distinction between firing and non-firing of the neurons, but instead the difference in the amount of firing. This theory is the basis for the current research being presented in this paper: the ability to transform the responses of certain stimuli by introducing other stimuli. Effective blocking of the taste receptors can be accomplished by either coating the surface pore or competing within the channel themselves to reduce the net effect of the bitter stimuli firings. While the introduction of competing stimuli is part of the masking system, specific flavours and sweetness profiles are essential to complete the experience and produce a pleasant taste for the consumer.(3-5)

There are number of factors that are taken into consideration during the taste-masking formulation like, Extent of the bitter taste of the active component, total dose of the drug, drug particulate shape and size distribution, Solubility and ionic characteristics of drug, formulations characteristics in terms of disintegration and dissolution rate, desired release rate and bioavailability and type of dosage form. (6-11)



Taste masking has always been the integral part of formulation especially for pediatric formulations. During almost last three decades advanced novel formulation techniques have been utilized to improve the aesthetics of the final products. The present review compiles the age old conventional methods as well as new techniques for taste masking.

Conventional methods:

Taste masking by amino acids, sweeteners, flavors and proteins

This techniques is the most simple and very old technique for improving taste characteristics of active component of the formulations. Taste masking can be achieved by using various amino acids like glycine, alalnine, leucine etc. Anticholesterolemic saponins containing foods, beverages along with pharmaceuticals are supplemented with amino acids for taste masking (12). Protein like compositions, useful for improvement of liver disorders, severe burn, trauma etc. containing branched amino acid can also be used for taste masking. Whey powder when treated with papain in the presence of amino acids ethyl L-leucine, ethyl L-iso leucine , ethyl L-valanine, cysteine hydrochloride and sodium carbonate in water at 40º C for 20 minutes resulted in tasteless and odourless powder(13). The taste of ampicillin improved markedly by preparing its granules with glycine and mixing them with additional quantity of glycine, sweeteners, flavours and finally compressing them into tablets (14,15) **.** Sweeteners like sucrose and its derivatives, sodium saccharin, aspartame, stevoside, monosodium glycyrrhizinate and flavouring agents like lemon water, vanillin, citrus etc. can be used to prepare syrup and drug can be evenly dispersed in syrup to prepare taste masked formulation. Starch and sorbitol as excipients with vanilla flavour, pork flavour and citrus flavour could be incorporated to mask the taste. Gelatin and flavouring agents mask bitter taste of tannic acid presumably by viscosity effect when made into a jelly by cooling (16). A gelatine gum like formula containing tannic acid, gelatine, chocolate flavour and water masked taste of tannic acid. Natural source based flavouring and perfuming agents are most widely used in pharmaceutical industry to mask the bitter taste of active component. The selection of flavouring agent should be complementary with sweetening agent and colouring agent in order to improve the aesthetics parameters to the formulations. (17,18)

Taste-masking by Increase in viscosity

The formulations prepared using viscosity imparting agents such as gums or carbohydrates can lower the contact with taste buds and diffusion of bitter substances from the saliva to the taste buds. This methods has been use for taste

masked liquid preparation containing relatively large amount of unpleasant tasting medicines. The composition of such a formulation comprises a taste-masking liquid base with a high viscosity induced by thickening agents such as polyethylene glycol and sodium carboxy methylcellulose. This type of formulations can incorporate higher amount of active ingredient then regular strength. For example, guaifenesin, which is normally administered in doses of not more than 100 mg in 5 ml of liquid, may be administered in doses of 200 mg/5 ml, without the feel of bitter taste.(19)

Taste masking using Lipids

Oils, surfactants and polyalcohols can effectively increase viscosity in the mouth and prevent contact of drug with taste buds. Taste masking of chloroquine was masked using the same principal. Multiple emulsions, O/W/O, containing paraffine as oil could mask bitter taste of chloroquine to some extent (20). Using glyceryl diester of C6- C22 fatty acid or diglycerine or sucrose fatty ester bitter taste of oral pharmaceuticals could be controlled. An aqueous solution containing quinine sulphate with diglyceride from rapeseed oil and sucrose with ester did not taste bitter. Hence, any excipient, which can impart viscosity in mouth and coating of taste buds, can successfully used for taste masking. Formulations with a large excess of lecithin or lecithin-like substances are claimed to control bitter taste in pharmaceuticals. Magnesium aluminum silicate with soybean lecithin is used to mask the unpleasant taste of talampicillin HCl. (21) Lipid coated pellets has also been studies for taste masking of hydrophobic drugs.(22)

Taste masking using anesthetic agents and taste potentiators

The taste buds can temporarily be anesthetized using local anesthetic agents like phenol and phenolic derivatives. These agents cause numbness of taste buds and hence the sensory buds will not be able to recognize the bitter taste. However, the time period for this numbness remains for 4 to 5 second. Fine powder of bees wax, sodium phenolate and active substance mixed with crosco vegetable oil, lime floss sugar and converted into lozenges. This formulation produced numbness of taste buds (23). Formulations like mouthwashes or cough drops like eucalyptus oil can be masked by adding frenchone , isoborneol , borneol.

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 (24)

Taste masking with salt preparation

Salt preparations have been successfully used to mask the taste by decreasing the solubility of drug into saliva or by altering the chemical group, which is responsible for bitter taste. Most salts of organic compounds are formed by the addition or removal of proton to form an ionized drug molecule, which is then neutralized with a counter ion. Penicillin prepared as the N-N' dibenzylethylene diamine acetate salt is a tasteless material. Magnesium salt of aspirin is almost tasteless. Bitter tasting decongestants, antihistamines, antitussive expectorants effectively taste masked using magnesium trisilicate/ fumed silica absorbate that is undetectable in mouth yet provides high degree of bioavailability. The unpleasant taste of water soluble Ibuprofen was masked by preparing alkaline metal bicarbonate salt of Ibuprofen (25-26).

Taste masking with effervescent formulations

Effervescent formulation contains components that can produce effervescence, like sodium bicarbonate, due to liberation of carbon dioxide. Sodium bicarbonate reacts with the acid when the effervescent preparation is added to water. The solution remaining after effervescence is known as carbonated water. The medicament dissolves in the carbonated water which serves to mask bitter, saline or nauseous taste of medicament. Studies carried out on effervescent granules of cetrizine showed better patient compliance (27)

Taste masking by Prodrug formulation of the drug

A prodrug is a chemically modified inert drug precursor that upon biotransformation liberates the pharmacologically active drug. 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. Prodrugs can be used to increase or decrease the aqueous solubility, mask bitterness, increase lipophilicity, improve absorption, decrease local side effects, and alter membrane permeability of the parent molecule (28) For example,. 7-7'succinylditheophylline. Erythromycin estolate. In aqueous solution, erythromycin exists as protonated form which has solubility in water. Lauryl sufate salt of Erythromycin estolate, a prodrug, is water insoluble. It does not impart bitter taste when comes in contact with taste buds unlike parent drug (29). The palmitate ester of chloramphenicol, a prodrug, used in pediatric suspension shows good patient

compliance. Some other examples include propoxyphen napsylate, tasteless and sparingly soluble derivative of Propoxyphen, clindamycin-2 palmitate, a prodrug of clindamycin. (30)

Coating Techniques

Coating is one of the most industry friendly processes for taste masking. Numbers of bitter drugs are formulated as coated dosage forms. In coating process, core material is coated with appropriate materials which prevents rapid release of the drug in saliva, but allow release of drug in the gastrointestinal tract where the drug is expected to be absorbed. Coating not only masks the taste but also improves patient compliance by improving aesthetic quality.

Coating with sugar solution is one of oldest technique for taste masking. Drug could be granulated along with hydrophilic vehicle and prepared granules can be coated with sugar to serve the purpose of taste masking. The study was carried out for masking the bitter taste of Cefeanal daloxate HCL. Granules of lactose and cornstarch containing Cefeanal daloxate HCL were prepared by using ethanolic solution of polyvinyl pyrrolidine and then coated with ethyl cellulose. They were further coated with coating solution containing lemon oil, sodium saccharine, and sucrose and hydroxypropyl cellulose. The prepared granules were evaluated and results showed good bioavailability and no bitterness (31). Protein solution could also be used as coating material. Aqueous whey protein solutions containing plasticizers, glycerol and sorbitol and maltodextrin as film formation promoting agent, were used as coating material for taste masking of bitter constituent (32)

Polymeric film coating is the most widely used industrial technique for taste masking. Various film formers like povidone, acrylate derivatives, Hydroxypropyl cellulose, Hydroxypropyl methylcellulose etc. can be used for coating. Film former like povidone gives clear, glossy and hard film while acrylates give transparent and elastic film (33). Bitter drugs in granules form can be coated with film formers to provide taste-masked formulation. Steryl alcohol and Eudragit 100 were used for taste masking of bitter macrolide antibiotic. The drug was mixed with molten steryl alcohol (at 70 °C) and Eudragit 100. The prepared mixture was spray granulated. The dried granules were mixed with sugar and HPC to give taste masked dry syrup (34). The same technique was used to mask bitter taste of quinidine using Eudragit E 100 as film former (35). In this technique quinidine sulphate was dispersed in water at room temperature with 4-8% sodium lauryl sulfate (SLS) and different hydrophilic and lipophilic plasticizers (7-15%). This wet mass was granulated and then

compressed to form tablets. Tablets were coated in a coating pan with Eudragit E 100 and characterized by disintegration and taste masking. Another coating technique was used for drug diphenhydramine. In this technique drug along with other diluents were milled and sieved to select core particles having size in between 63-212 micron. Core particles were coated with various polymers like Surelease, Aquacoat, Ethocel 7,10, 45 & 100, and Eudragit E 100 with suitable plasticizer (36).

Taste masking of ibuprofen has been successfully achieved by using the air suspension coating technique to form microcapsules, which comprises a pharmaceutical core of a crystalline ibuprofen and methacrylic acid copolymer coating that provides chewable taste masked characteristicsHigh molecular weight lipid excipients can be used in hot melt coating technique for drug like Ibuprofen. In this technique lipid excipients glyceryl behenate is mixed with surfactant Labrasol™ and Ibuprofen was coated using above prepared blend in a top spray fluid bed coater. Lipid coated granules were mixed with microcrystalline cellulose and filled either in capsule or can be directly compressed to prepare tablet, serves purpose of taste masking of Ibuprofen (37)

Microcrystalline cellulose based pellet containing bitter drug can also be coated to achieve taste masking. Studies based on microcrystalline cellulose-based pellets (315-710µm) containing different quinine sulphate concentrations prepared by extrusion-spheronisation and then coated with an aqueous suspension of Eudragit® EPO, dibutyl sebacate or stearic acid in a fluid bed coater resulted in acceptable taste and texture. The adsorbates of bitter drugs like metha pyrilene were coated with 4:1 ratio of ethylcellulose HPMC mixture and the results showed reduction in bitter taste of active drug (38).

In some cases taste masking along with fast onset of action is required, thus novel technique was developed for taste masked orally disintegrating tablet. In this technique active ingredient with bitter taste was dissolved in water and mixed with silica. Drug adsorbed on silica was introduced in fluidized bed granulator and coated with polymer. Granules were produced by wet granulation of sugar alcohols, sweeteners and flavor with binder solution. The mixture obtained by this method was taste masked can be compressed in to tablet (39). Fast disintegrating, taste masked product can be prepared by using WOWTAB technology. Active pharmaceutical ingredient retained on #80 mesh, coated with Aquacoat plasticized with triacetin in the Wurster air suspension column and then coated API was incorporated into WOWTAB technology containing polysaccharides, lubricants, sweeteners and flavours. Results showed fast disintegration and

masking of taste (40)

Novel techniques like DUPONT can also serve the purpose. The same technique was used for coating of small individual particles that are below 50 microns and even down to a few microns. Here particles with API can be coated with polymers, surfactants, and other materials to modify their bitter taste (41)

There are certain polymers, which on combination showed more viscous form then their individual forms. This synergetic interaction is enhanced when the polymers are combined under supercritical conditions. This technique not only provides taste masking but also enhance drug loading as a result of enhanced exposure of hydrophobic domains (layer) within the polymer structure. In one experiment, pullulan and carboxymethyl cellulose, which on combination showed more viscous form then their individual forms. This polymeric solutions were combined along with drug particles under supercritical conditions like liquid CO2, 35°C and 80atm, maintained in the reactor with stirrer forming solid films around the bitter drug particles when solvent was evaporated (42)

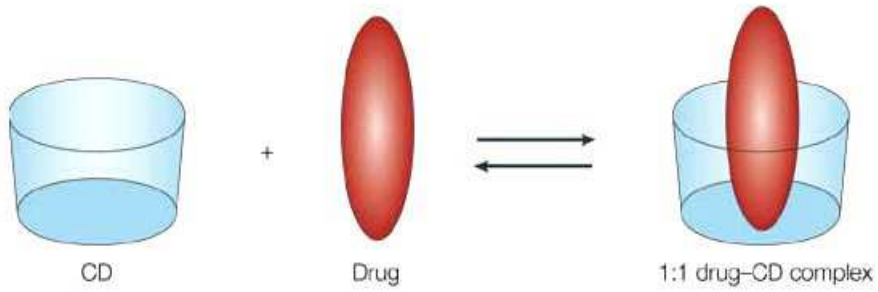
Taste masking by solid dispersion

The solid dispersion of one or more drugs in an inert carrier of solid state is prepared by physical mixing, co-grinding or by solvent evaporation method. Inert carriers that can be used for solid dispersion preparation are sugar carriers like sucrose, galactose, dextrose, trehalose, Various PEG derivatives or PVP. Here the drug is entrapped in carrier, so it prevents the contact of the drug with the taste buds. The mass of the drug griseofulvin was prepared using malt dextrin as a hydrophilic carrier by common solvent method or melting method followed by drying in dessicator over anhydrous CaCl2, and then product is crushed, pulverized and sealed. The resulted formulation was taste masked(43) The above-mentioned method was used for masking the bitter taste of anti histaminic i.e. femotidine also. The bitter drug femotidine and sugar alcohol and were mixed and the mixture was processed to form solid pharmaceutical preparation (44) The model bitter drugs Acetaminophen, ketoprofen and trypsinogen were also successfully masked by using Polyethylene glycol (PEG), Eudragit RS (EU) and lipid tripalmitin (TP) as excipients. An excipient and a drug (typically 50% drug loading, 10.0 g batch) were plastisized and then mixed with supercritical CO_2 at operating pressure between 200 – 300 bar and temperature between 40 – 55°C. This resulted into polymeric mixtures with taste-masked formulation. (45)

Solid dispersion prepared by malt extrusion can also be used for taste masking of drugs like Verapamil hydrochloride using methacrylic acid copolymer EUDRAGIT® as matrix former. The powders were fit separately into a twin-screw extruder, processed above the glass transition temperature of the polymer and finally milled. As a result the intensity of the bitter taste was reduced significantly. This is a more preferable technique than film coating in case where small particles are needed.(46-49)

Taste masking using inclusion complex

This is the one of the latest and current technique for the taste masking with beneficial advantage of enhanced solubility of poorly soluble drug. Complexation of drug with complexing agent modifies the biopharmaceutical parameters like drug dissolution rate and thus it masks the bitterness of the drug. Cyclodextrin (CD) is the most widely used complexing agent. Cyclodextrins are cyclic oligosaccharides, which have the ability to form host/guest inclusion complex both in solution and in solid phase. Molecules or functional groups that cause unpleasant taste can be hidden from the sensory receptors by encapsulating them within the cyclodextrin cavity. These complex molecules are strongly hydrated on the outer surface thus they do not get attached to the taste bud. Various types of cyclodextrins are used for complexation according to the property of drug eg. Beta cyclodextrin, gama CD, hydroxypropyl βCD, methyl βCD etc. Reconstituted suspension of the CD-drug complex can be prepared for pediatric and geriatric patients. The drug: CD complex can also be directly compressed to prepare orodispersible tablet when fast onset of action of bitter drug is required(50-52)



.

Physical mixture of drug and beta cyclodextrin was prepared using high shear mixing and phase solubility study showed strongest binding of drug with beta cyclodextrin and results in taste masked formulation (53) Dextromethorphen was taste masked using same polymer complexation technique. The taste-masked Dextromethorphan formulation was prepared by wet complexation of the active ingredient and cyclodextrin in solution, which is then dried to form

taste-masked complexed drug powder. The drug powder was mixed with flavors, film-forming polymers, and solvents, on a carrier substrate, which provided an improved taste masking formulation. Complexes of caffeine and organic acids formed by rapidly cooling individual hot aqueous solution of caffeine and gentisic acid and the resulting micro crystalline powder precipitate was washed with H_2O and dried under vacuum at 80°C and finally packed giving taste masked formulation. (54)

Taste masking by Ion exchange resin

Ion exchange resins are high molecular weight water insoluble polymers and so are not absorbed by the body and therefore inert and safe for use. Ion exchange resins have either acidic or basic functional group and they can be broadly classified as strong acid cation exchange resin (Amberlite IRP-69), Weak acid cation exchange resin (Amberlite IRP –65, carbopol 934 P, Kyron T-114), Strong base anion exchange resin (Amberlite IRP-276), Weak base anion exchange resin (Dimethylamine resins).

The complex of cationic drug and weak ion exchange resin does not break at pH of saliva but at high cationic concentration in stomach free drug is immediately released. Thus while passing through mouth, the drug remains in complex form and thereby imparting no bitter taste in the mouth. The peripheral vasodilator buflomedil was be taste masked by bonding to a cation exchange resin such as Amberlite IPR 69 at 60% resinate powder. The Amberlite IRP 64 resin powder is also recommended with isopropyl alcohol as solvent. The dried powder was incorporated into oral formulation. The same technique was used in order to formulate taste-masked formulation of clarithromycin. Ion-exchange resin complex was prepared by dispersing clarithromycin in cacao fat at 35 to 50°C and atomizing to get fine granules and then suspended in of poly vinyl acetate diethyl amino acetate at 0°C , spray dried and tested for taste masking. The results showed good bioavailability and no bitter taste. Complex of diphenhydramine with polyglutamic acid was found to be stable in acidic solutions but dissolved gradually as solution pH increased and thus taste of the drug was masked in mouth. Drug-resin complex dissolves completely in a pH=7.4 solution within 5~10 minutes. The ion exchange resin drug complex can be compressed to prepare orodispersible tablet for drugs like levocetrizine dihydrochloride. In this technique the drug resinate complex was prepared by dispersing drug solution in resinate solution, Tulsion 335, for 360 minutes at various temperature between 25º C- 80º C and then filtered through whatman

filter paper. Solvates were evaporated to get dry powder. The dried drug: resin complex powder was then compressed to form orodispersible tablet. Here, the drug, which gets disprsed in mouth, will not show any bitterness due to its complexation with resin molecule. (55-59)

Nanotechnology based taste masking techniques

Microencapsulation

Microencapsulation is a modified form of film coating differencing only in the size of the particle to be coated and the methods by which coating is achieved. The bitter drug particle is held in the polymer matrix or polymer film and thus taste of drug can be successfully masked. A number of polymers have been successfully used in microencapsulation technique includes gelatine, polyvinyl alcohol, ethyl cellulose, cellulose acetate phthalate and styrene maleic anhydride. Microencapsulation can be achieved by phase coacervation, polymerisation, solvent evaporation and ionisation. Bitter taste of Enoxin was masked by using novel microencapsulation process. The microencapsulation was achieved by wet spherical agglomeration along with modified phase seperation coacervation method. The bitter taste of chloroquine diphosphate was masked by microencapsulation technique, in which coating materials were obtained from Vinyl pyridine compounds and microencapsulated products formulated in suspension and found to have acceptable taste(60) Microencapsulation using phase coacervation was used for model bitter drug Beclamide(61) Conventional chewable and effervescent tablets were prepared from microencapsulated drug using gelatine as a polymer. Incubation of unmodified cornstarch in aqueous solution of drug and converting them into microencapsulated particles could also mask the taste of bitter drug. Diphenhydramine (DPH) was incubated with starch at different temperatures (35 to 55^0C) for different time periods (1 to 4 hours). DPH-loaded starch particles were then dried and results revealed taste masking of parent drug. Taste masking can be achieved by combination of encapsulation and CO_2 based techniques. Acetaminophen and pseudoephedrine hydrochloride (PE) were used as model bitter drug and different Eudragits, ethyl cellulose (EC), cellulose acetate (CA) with different plasticizers and emulsifying agents as excipients for encapsulation. Coated particles were mixed with super critical carbon dioxide (at 35-65°C and 100bar) and composite polymeric particles (50–300mm) showed sustained release and some taste masking (62)

A new reverse enteric polymer, which collapses above pH 4 unlike Eudragit E, which is permeable above pH 5, was conceptualized and synthesized. Taste masking of cefuroxime axetil was evaluated by polymeric encapsulation. Polymers inhibited polymorphic transformation of cefuroxime axetil, which led to the coclusion that the new reverse enteric polymer provides new technology platform for formulating taste masked and immediate release products such as granules, film coated / ODT and chewable tablet. (63)

Nanoparticle is a submicroscopic solid particle with a size ranging from 10 nm-1 µm. Polymers that can be used for preparation of nanoparticles includes albumin, ethyl cellulose, casein, gelatin, polyesters, polyanhydrides and polyalkyl cyanoacrylates. As the drug particles are individually coated they prevent drug contact with taste bud and thus mask bitter taste of drug. Those nanoparticles can also be delivered in form of nanosuspension or nanoemulsion for pediatric and geriatric patients. Nonotechnology can be used for taste masking of fish oils, salts, alkaloids, clofibrate and sulfa drugs. (64,65)

Lipid nano particles containing omega –3 fatty acids as an alternative of fish oil capsules were developed. Lipids like Dynasan 118 and adipic acid were used with sodium dodecyl sulfate (SDS), TPGS and polyvinylpyrrolidon (PVP) are used as stabilizers. Lipid nanoparticles were prepared by high-pressure homogenization using a Micron LAB 40 (APV Homogenizers, Unna, Germany). Further addition of citrus food flavour covered taste and odour, which further represents an easy swallowable formulation with taste masking effect.(66)

Neural technique can also be used for taste masking. In this technique heat-sensitive model drug with strong bitter taste was selected. Injecting the suspensions containing drug substance and different levels of cellulose type polymers with plastizers into spray dryer developed fine particles. That fine particles resulted in to taste masked formulation.

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. Multiple emulsions is 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. o/w/o emulsion is a type of multiple emulsion 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.

Conclusion

Numbers of herbal origin and chemically synthesized active therapeutics have bitter taste. With the advent of novel formulation techniques as well as novel excipients, the bitter and unacceptable taste can be masked successfully. Formulation attributes in terms of taste, texture and appearance can now be modified to impart better formulation asthetics. Sugar coating, syrups, lipids, amino acids, proteins are very widely used excipients for taste masking Though the number of polymers are available for film coating, sugar coating technique yet remain versatile in herbal industry. This is mainly due to cost effectiveness and use semi pure extracts in formulation, which has unacceptable colour. Film coating has additional advantage of making the formulation pH dependent and thus targeting the drug release at desired site of gastro intestinal tract. Apart from sugar coating and film coating techniques, compression coating method can also be adopted. Use of hydrophilic polymers for coating, solid dispersion, complexation, and hot melt extrusion are the most widely explored methods in pharmaceutical industry. Ion exchange resins adsord the drug and form complex. Dry syrups and orodispersible formulation containing ion exchange resin can be formulated for geriatric and paediatric patients. In the era of nano technology, drug can be converted to nanoparicles. Polymer coated nanoparticles can be delivered in form of nano suspension and nano emulsion.Neural network technique is one of latest optimising methodology. The formulation parameters as well as polymers can be screened for optimum results.

References

1. Lachman L, Lieberman H.A., kanig J.L. Liquids. In The Theory and Practice of Industrial Pharmacy. Pheladelphia: Lea and Febiger; 1987. p. 470,419.

2. S. B. Ahire et. al, A REVIEW: Taste masking techniques in pharmaceuticals, An Intrernational Journal of Pharmceutical Science. (online) 2011.
3. Smith DV, Margolskee RF. Taste fundamentals. Scientific American 136 (2001) 26-33.
4. Kinnamon SC, Margolskee RF. Mechanisms of taste transduction. Curr Opin Neurobiol 6 (1996) 506-513.
5. Lindemann B. Taste reception. Physiol Rev 76 (1996) 719-766.
6. Gupta A.K. et. Al International Journal of Drug Delivery Technology 2010; 2(2) 56-61, Practical Approaches for Taste Masking of Bitter Drug: A Review).
7. Shalini Sharma.,Shaila lewis., Taste masking technologies: a review.,International Journal of Pharmacy and Pharmaceutical Sciences,2010; 2(2):6-13.
8. Zelalem Ayenew., Vibha Puri., Lokesh Kumar., Arvind K. Bansal., Trends in Pharmaceutical taste masking technologies: A patent review., Recent Patents on Drug Delivery & Formulation, 2009;3:26-39.
9. Vijay D. Wagh., Shyam V. Ghadlinge. Taste masking methods and technologies in oral pharmaceuticals: Current Perspectives., Journal of Pharmacy Research, 2009;2(6):1049-1054.
10. Y. Deepthi Priya ., Y.A.Chowdary., T.E.G.K.Murthy,, B.Seshagiri., Approaches for taste masking of bitter drugs: A Review., Journal of Advances in Drug Research, 2011; 1(2): 58-67.
11. Jha Kumar Sajal., Sharma Raj Uday., V Surendra., Taste masking in Pharmaceuticals : An update., Journal of Pharmacy Research, 2008; 1(2):126-130).
12. K.P.Sampath Kumar et.al., Recent trends in taste masking of bitter drugs, Journal of drug delivery research, issue 1, 2012.
13. S.Watabe, T.kati, N.Nergata,"Bitterness free drug composition containing amino acids", JP04, 207,161 toRonto Pharmaceutical co.Ltd. (1992).
14. Pokharkar, Versha B. 2005. Taste Masking of Pharmaceuticals. Pharmaceutical Reviews E-Journal. 3(2).
15. A Nanda, R. Kandarapu and S Garg, *Indian J Pharm Sci*, Vol. 64, No. 1, pp. 10-17, 2002.
16. G V M Babu, K Himasankar, C P S Narayan and K V R Murthy, *Indian J Pharm Sci*, Vol. 63, No. 5, pp. 408-412 , 2001).

17. E L Parrot, Theory and Practice of Industrial Pharmacy (Eds. L Lachman, H A Liberman and J L Kanig), Varghese Publishing House, Mumbai, pp. 21-25, 1987.) .
18. S.Micura, M.Matshushita & T.Fujinaga's "Bitterness free syrups containing oils, surfactants and polyalcohols"in Can.pat.Appl C.A.2, 082, Mc Neil PPGInc. (1992).
19. James Swarbrick & James C. Boylan"Flavors and Flavor modifiers" Encyclopedia of Pharmaceutical Technology (4), 101-132
20. Vijay A. Agrawal, Aditya P: Taste Abatement Techniques To Improve Palatability Of Oral Pharmaceuticals: A Review. International Journal of Pharmaceutical Research And Development 2008; Vol 2: 22-30).
21. Rao, M.Y.., Bader, F. Masking the taste of chloroquine by preparing multiple emulsions. The Eastern Pharmacists. 1991; November: 123-124.
22. Pokharkar, Versha B. 2005. Taste Masking of Pharmaceuticals. Pharmaceutical Reviews E-Journal. 3(2).
23. Jonathan Vaassen et. Al,Taste masked lipid pellets with enhanced release of hydrophobic active ingredient, International Journal of Pharmaceutics, Volume 429, Issues 1–2, 15 June 2012, Pages 99–103.
24. R. C. Fuisz. Taste masked Medicated Pharmaceutical. U.S. Patent 1991, 5028632.
25. .Shalini Sharma.,Shaila lewis., Taste masking technologies: a review.,International Journal of Pharmacy and Pharmaceutical Sciences,2010; 2(2):6.
26. Glazko et al**.,** Antibiot. Chemother. 2, 234 (1952).and Jumao-as et al**. .....** Chloramphenicol esters and method for obtaining same, US Patent 2662906, 1953.
27. . Gargely, G.; Gargely,T.; Gargely,I. Pharmaceutical Preparation in the Form of an Effervescent and/or Disintegrating Tablet or an Instant Granule and Process of Producing It. PCT Int. Appl. WO9313760, July 22,1993.
28. [B. M. Maurin. Dosage Form Design: A Physicochemical Approach. Encyclopedia of pharmaceutical technology, third edition 2007, 1, 939-947.].
29. Brahmankar D M. and Jaiswal S B. Biopharmaceutics and pharmacokinetics, 1stEd. Vallabh Prakashan, New Delhi1995; 162-163.
30. Tammara, V. K., Narurkar, M. M., Crider, A.M., Khan, M.A., J Pharm Sci. 1994, 83 (5),644-648.

31. Sharma S, Lewis S: Taste Masking Technologies: A Review. *International Journal of Pharmacy and Pharmaceutical Sciences* 2010; Vol 2, Issue 2:25-33.17. T.Sakakibara"Bitterness Free Lopamide Tablets with Sugar or Film Coating" in JP 05, 04,291 to Kanebo Ltd.(1993)

32. Natalja Genina, Heikki Räikkönen, Henrik Ehlers, Jyrki Heinämäki, Peep Veski, Jouko Yliruusia, Thin-coating as an alternative approach to improve flow properties of ibuprofen powder, International Journal of Pharmaceutics Volume 387, Issues 1–2, 15 March 2010, Pages 65–70
33. Sharma S, Lewis S: Taste Masking Technologies: A Review. *International Journal of Pharmacy and Pharmaceutical Sciences* 2010; Vol 2, Issue 2:25-33.17.
34. T.Sakakibara"Bitterness Free Lopamide Tablets with Sugar or Film Coating" in JP 05, 04,291 to Kanebo Ltd.(1993)
35. C.M. Bakke, L. Anderud, A. Aslaksen; Acta Med. Scand. 207:183 (1980).
36. P.C. Kayumba et al (2005) Taste-masked quinine pamoate tablets for treatment of children with uncomplicated *Plasmodium falciparum* malaria, International Journal of PharmaceuticsVolume 392, Issues 1–2, 15 June 2010, Pages 29–34
37. Shen R.W., US Patent, 1996, 5,552152).
38. Borodkin S, Sundberg DP. "Polycarboxylic acid ion-exchange resin adsorbates for taste coverage in chewable tablets", J Pharm Sci., 1971;60:1523– 1527.)
39. 24. Fu; Yourong , Pai; Chaul Min , Park; Sang Yeob , Seomoon; Gun , Park; Kinam Highly plastic granules for making fast melting tablets US Patent application 10/841,979 May 7, 2004.
40. Sharma V, Chopra H: Role of Taste And Taste Masking of Bitter Drugs In Pharmaceutical Industries: An overview. *International Journal of Pharmacy and Pharmaceutical Sciences* 2010; Vol 2 (4):12-18.
41. T. J. Trout, N. Gangrade, E. Gommeren, and L. Berger, DuPont's novel particle technology to enhance pharmaceutical compounds, DuPont's website, accessed on 6th june 2012
42. Shirai Y. A novel fine granule system for masking bitter taste. Chem Pharm Bull 44 (1996) 399-402
43. Roy GM: Taste masking in oral pharmaceuticals. *Pharm. Tech*. 1994; 18: 84-99).

44. T.hayashida & M.Hatayama,"Carbohydrates as taste masking agents for oriental to drugs", in JP 05 17,372 to Yoshitomi Pharmaceutical IndustriesLtd. (1993).
45. Chauhan B, Shimpi S, Paradkar A. Preparation and characterization of etoricoxib solid dispersions using lipid carriers by spray drying technique. AAPS Pharm Sci Tech 6 (3) (2005) 405-412.
46. Breitkreutz J, Bornhöft M, Wöll F, Kleinebudde P. Paediatric drug formulations of sodium benzoate: I. Coated granules with a hydrophilic binder. Eur J of Pharm and Biopharm 56 (2003) 247-253.
47. Breitkreutz J, Firas El-Saleh, Christian Kiera, Kleinebudde P, Wiedey W. Paediatric drug formulations of sodium benzoate: II. Coated granules with a lipophilic binder. Eur J of Pharm and Biopharm 56 (2003) 255-260.
48. *Kulkarni, Mohan Gopalkrishna and Menjoge, Anupa Ramesh. Taste masked pharmaceutical compositions comprising bitter drug and pH sensitive polymer. WIPO PatentApplication, O/2005/055987,2005.*
49. Chaudhari, P. D. 2006. Current trends in solid dispersion techniques. Pharmaceutical Reviews E-Journal. 1(12)
50. *Sajal JK, Taste Masking In Pharmaceuticals An update. Journal of pharmacy research 2008; vol 1, issue 2, 126-130.32 , .*
51. H. Sohi, Y. Sultana, and R. Khar. Taste masking technologies in oral pharmaceuticals: Recent developments and approaches. Drug Dev. Ind. Pharm. 30:429–448 (2004).
52. Hayward, M., U.S. Patent, 37277, 1998
53. *Ozer, A.Y. and Hincal, A.A. 1990. Fast dissolving Drug Delivery System: An update. J Microencapsulation. 327-330.*
54. Motola, S., Agisim, G, R., Mogavero, A.., U.S. Patent 5024997, 1991. Ueno, M., Japan Patent, 0411865, 1992
55. Jha Kumar Sajal., Sharma Raj Uday., V Surendra., Taste masking in Pharmaceuticals : An update., Journal of Pharmacy Research, 2008; 1(2):126-130
56. Dorfner, K. " Ion Exchanger Properties and Applications" Third Edition, Ann Arbor Science Publisher, 1972, 2.
57. Jain, N.K.; "Advances in Controlled and Novel Drug Delivery", First Edition, 2001, PP 290-306.
58. Borodkin, S.; Yonker, M.H.; Journal of Pharmaceutical Sciences; 1970, 59(40), 481.

59. Sambhaji Pisal, Ranna Zainnudin, Praddin Nalawade, Kakasaheb Mahadik and Shivajirao Kadam. " Molecular Properties of Ciprofloxacin Indion 234 Complexes", AAPS Pharm.Sci.Tech, 2004 ;5(4).
60. Ndesendo V. M. K., Meixner W.Microencapsulation of chloroquine diphosphate by Eudragit RS.100. J. Microencap. 1996; 13: 1-8).
61. Ozer, A.Y.;Hincal. A.A. Studies on the masking of unpleasant taste of beclamide: microcapsulation and tableting. J. Microencasul 1990.7(3), 327-339.
62. Hoy, M.R.; Roche, E.J. Taste Mask Coating for Preparation of Chewable Pharmaceutical Tablets. Eur. Pat. Appl. EP0523847, January 20, 1993.
63. Lorenzo-Lamosa, M.L.; Kuna, M.; Vila-Jato, J.L.; Torres, D.; Alonso, M.J. Development of microcapsulated form of cefuroxime axetil using pH-sensitive acrylic polymers. J. Microencapsul 1997, 14(5),660-616
64. Al-Omran, M.F.; Al-Suwayeh, S.A.; El-Helw, A.M.; Saleh, S.I. Taste masking of diclofenac sodium using microencapsulation. J. Microcapsul 2002,19(1), 45-52.
65. Jin, Y.; Ohkuma, H.; Wang, C.F.; Natsume, H.; Sugibayashi, K.; Morimoto, Y. Pharmaceutical evaluation of fast-disintegrating tablet containing nicorandil-loaded particles. Yao Xue Xue Bao 2001,36(7), 535-538.

Corresponding Author:
Dr. Munira Momin*
Email: *momin_munira@hotmail.com*