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Review Article

Taste masking potential of bitter drugs: A Review

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Abstract

Taste masking of liquid formulation present a major challenge because the majority of pediatric Preparations are syrups and suspensions. Taste is a critical factor in development of oral dosage form. Taste masking is important for bitter drugs to improve the patient compliance especially in the pediatric and geriatric populations. The field of taste masking of active pharmaceutical ingredients (API) has been continuously evolving with varied technologies and new excipients. Two approaches are commonly utilized to overcome the bad taste of the drug. The first includes reduction of drug solubility in the saliva and second approach is to alter the ability of the drug to interact with taste receptor. Conventional taste masking techniques such as the use of sweeteners, amino acids and flavoring agents alone are often inadequate in masking the taste of highly bitter drugs. The recent techniques of taste masking are dispersion coating, granulation, solid dispersions, inclusion complexation, ion exchange resin approach, mass extrusions technique, spray drying, microencapsulation, liposomes, prodrugs, salt formation, adsorption, wet spherical agglomerations, multiple emulsions, gel formation, effervescent technique and continuous multipurpose melt technology. Evaluation of taste concealed formulation is done by panel testing, measurement of frog taste nerve response, multichannel taste sensor and spectrophotometric method.

Keywords: - : Taste masking, solid dispersions, taste sensor, panel testing.

INTRODUCTION

Objectionable taste is the one of the most important formulation problem that is found in certain bitter drugs. The oral administration of bitter drugs is the major concern for patient compliance. In the case of pediatric and geriatrics patient, unpleasant taste should be avoided and leading to noncompliance which result in decrease therapeutic efficacy. In the present scenario, this bitter and unpleasant taste of drugs clash to the pharmacist [1]. Taste is an important factor in the development of a dosage form. Tastes can be categorised into five primary taste qualities: sweet, sour, salty, bitter, and umami or savory. Within hours after birth, the infants reject bitter tastes and prefer sweet and umami tastes. Children have a much greater number of taste buds than adults which are responsible for sensitivity towards taste. These taste buds regenerate every two weeks. As with many of the senses, taste becomes altered as a function of the aging process, which explains why most children find certain flavors to be too 'strong' when adults do not [2]. There for taste masking of bitter drugs is very important. The word flavor refers to a mixed sensation of taste, touch, smell, sight and sound, all of which combine to produce an infinite number of gradations in the perception of a substance. The four primary tastes – sweet, bitter, sour and saline; appear to result from physicochemical and partly from psychological action [3].

Taste and its physiology

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 [4].

Taste Buds

Taste buds are small sense organs in most vertebrates, helps in the detection of taste. Hence there are a group of cells, found especially on the tongue. Taste buds have been identified on the soft palate, pharynx, epiglottis, which allow different types of tastes to be **recognized.**

Salty taste (edge and upper portion):

The salty taste is one among the five taste receptors of the tongue. They are located on the edge and upper front portion of the tongue.

Sweet taste (tip):

The sweet taste is one among the four taste receptors in the tongue. They are found on the tip of the tongue.

Sour taste (along sides in back):

The sour taste is also one of the four taste receptors of the tongue. They occur at sides of the tongue and are stimulated mainly by acids.

Bitter taste (back):

The bitter taste is the last and one of the four taste receptors in the tongue. It is located towards the back of the tongue. It is stimulated by a variety of chemical substances, most of which are organic compounds, although some inorganic compounds such as magnesium and calcium also produce bitter sensations [5].

Ideal properties of taste masking process

An ideal taste masking process and formulation and characterization should have the following properties.

•Involve least number of equipments and processing steps.

•Require minimum number of excipients for an optimum formulation.

•No adverse effect on drug bioavailability.

•Require excipients that are economical and easily available.

•Least manufacturing cost.

•Can be carried out at room temperature.

•Require excipients that have high margin of safety

•Rapid and easy to prepare [6].

Factors affecting selection of taste masking technology

1) Extent of the bitter taste of the API.

2) Required dose load.

3) Drug particulate shape and size distribution.

4) Drug solubility and ionic characteristics.

5) Required disintegration and dissolution rate of the finished product [7].

1. Extent of Bitter Taste

In case of bad tasting medicaments even a little exposure is sufficient to perceive the bad taste. Use of different technologies depends on the extent of bitterness of the drug. For very bitter drugs simple techniques like use of sweeteners, flavors, adsorbates are not sufficient so technologies like coating, use of resins, microencapsulation, and viscosity enhancers can complement the taste masking efficiency.

2. Dose of Active Pharmaceuticals

Dose of a drug may dictate whether a particular formulation strategy would be suitable to achieve taste masking. In pediatric formulations, the dose is small enough so as to allow the usage of simple techniques like flavoring agents; sweetners etc. For higher doses, technologies like coating, use of resins, microencapsulation, and Viscosity enhancers are to be used.

3. Dosage Forms

It is estimated that 50% of the population have problem of swallowing tablets, especially the pediatric and geriatric population. Chewable tablets and liquid oral dosage forms have been used to address these problems. However, it is difficult to formulate some drugs in these dosage forms due to their poor palatability.

4. Drug Solubility

Physicochemical properties of drug play an important role in the selection of taste masking technology, for example, ondansetron has a relatively low water solubility at higher pH, based on which a rapidly disintegrating taste masked composition of ondansetron was formulated by adding an alkalizing agent to reduce the water solubility and consequent taste perception.

5. Ionic Characteristics of Drug

Ionic characteristics of drugs govern the selection of ion exchange resin polymers and the suitability of drug

candidate for this technology. For example, anionic polymers are good candidates for cationic drugs like donepezil hydrochloride, and the cationic polymers are choice of excipients for anionic drugs [8].

Taste masking techniques

To achieve the goal of taste abatement of bitter or unpleasant taste of drug, various techniques are reported. These are as follows:

1.Addition of flavoring and sweetening agents
2.Microencapsulation
3.Ion-exchange
4.Inclusion complexation
5.Granulation
6.Adsorption
7.Pro drug approach
8.Solid dispersion system
9.Multiple emulsion technique
10.Miscellaneous [9].

Addition of flavoring and sweetening agents

A combination of flavoring agents is usually employed. Flavor adjuvants like menthol and chloroform are considered as a desenstizing agents because addition to their own odor and flavor they also have mild anaesthetic 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. A survey of the taste preferences of human race, as a whole, indicates that sweet taste is very aggreeable 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 1 presents a compilation of the most common artificials and natural sweeteners used in pharmaceutical products, their relaive sweetness levels, and pertinent comments.

Taste masking by microencapsulation

It is important to understand that only soluble portion of the drug can generate the sensation of taste. And it is possible, or even likely, that coating the active drug with a properly selected polymer film can reduce its solubility in saliva in thus taste could be masked. Coating the drug particles created a physical barrier between the drug and the taste buds and this taste of active could be masked. Microcapsules are made up of a polymeric skin or wall enclosing a core.

Microencapsulation is a processs by which very tiny droplets or particles of liquid or solid material are surrounded or coated with a film or polymeric material.

Table 1: Relative sweeteness of commonly used sweeteners

Sweetening agents	Relative sweeteness	Comment
Aspartame	200	Not very stable in solution
Acesulfame Potassium	137-200	Bitter after taste if used in higher concentration
Cyclamate	40	Banned
Glycerrhizin	50	Moderately expensive
Lactose	0.16	Large amount required
Mannitol	0.60	Negative heat of solution
Saccharin	450	Unpleasent after taste
Sucrose	1	Most commonly used
Sucralose	600	Synergestic sweetening effect

Advantages

•Taste masking can be achieved with the desirable fast or controlled drug release.
•Bitter liquids may be coated to convert them to solid particles.
•The coated bitter particles can adapt to a wide variety of dosage forms and product applications.
•The goal of microencapsulation may be accomplished by any of the following techniques
•Air suspension coating
•Coacervation-phase separation
•Spray drying and spray congealing
•Solvent evaporation
•Multiorifice- centrifugal process
•Pan coating
•Interfacial polymerization [10].

Taste Masking by Ion Exchange Resins

Based on Complexation of drugs with ion exchange resins. Ion exchange resins are water insoluble, cross linked high molecular weight polyelectrolytes containing salt forming groups in repeating position on the polymer chain which exchange their mobile ion of equal charge with the drug molecule. As taste perception of bitter drugs is experienced in the mouth at taste buds, complexed drugs resinate does not release drug in mouth due of scarcity of exchangeable ions (at pH 6.7) in the saliva and when complex comes in contact with GIT fluids (at acidic pH), complex is broken down quickly and drug is release. Resins being polyelectrolyte have extensive binding sites leading to very high drug loading ability. Ion exchange resins have received considerable attention because of their versatile properties as drug delivery vehicles, chemically inert and free from local and systematic side effect possess long-term safety even while the tablet

ingesting large doses and also compatible with all conventional solid, semisolid.

Table-2: Commonly used ion exchange resins

Type	Functional group	Matrix structure	Taste masked drugs
Weak cation	-COOH	Methacrylic Acid Divinylbenzene	Norfloxacin, Ofloxacin, Roxithromycin
Strong cation	-SO3H	Polystyrene Divinylbenzene	Chlorpheneramine maleate, Ephedrine Hydrochloride
Weak anion	N-R2	Polystyrene Divinylbenzene	NTM
Strong anion	N-R3	Polystyrene Divinylbenzene	NTM

Inclusion complexation

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 complexes4-11. β- cyclodextrin is widely used complexing for taste masking of drugs due to its sweet taste and is non toxic in nature. Table no: 3 is a literature report of various complexing agents used for taste masking of bitter drugs [11].

Table 3: Literature report on taste masking by inclusion complexation

Drug	Category	Dosage form	Complexing agent used
Zinc acetate dehydrate	Recover zinc deficiency		Anethol -β-cyclodextrin complex and saccharin
Carbapentane citrate	Local anesthatic	Oral liquid	Cyclodextrins
Ibuprofen	NSAIDS	Solution	Hydroxypropyl β- cyclodextrin
Gymnema sylvestre	Antidiabitc	Oral liquid	β- cyclodextrin, Chitosan
Dioscin	CVS Disorder		β- cyclodextrin
Benexate hydrochloride	Antiulcer	Granules	β- cyclodextrin
Metronidazole benzoate	Antibacterial		γ- cyclodextrin

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 preparation. As these polymers are insoluble in saliva, thus the bitter taste of the drug can be masked. The taste masked granules can also be formulated as chewable tablet and rapidly disintegrating tablets.

Table 4: Examples of drugs taste masked by granulation technology are enlisted in table

Drugs	Granulating agent	Percentage of excipient used	comment
Erythromycin	Alginic acid	Drug : polymer Ratio of 2.5:1 to 50:1	Taste masked granules, which can be formulated asdry syrup suspensions/chewable of dispersible tablets
Dextromethorphan	Cyclodextrin	Drug : polymer Ratio of bet ween 0.9:1 and 1:25	Mixing of drug with Cyclodextrin followed by granulation wit hout complexation
Ibuprofen	Mixing of drug with Cyclo dextrin followed by granulation; without complexation	Ratio of drug to MCC is 7 0:30 to 90:10 w/w	A simpler and more effective process compared to coating
Calcium compound	Sugar alcohol	-	-
Erythromycin	Alginic acid	-	-
Norfloxacin	Meth acrylic acid ester	-	-
Ondansetron	Polyacrillin Potassium	-	-

Table 5: Examples of drugs and adsorbent used in adsorption technique

Drug	Adsorbent
Ranitidine	Magnesium trisilicate
Dextromethorphan hydrobromide	Magnesium trisilicate
Trimethoprim	Magnesium aluminium silicate(veegum F)
Loperamide	Magnesium aluminium silicate(veegum F)
Phenyl propanolamine	Magnesium aluminium silicate(veegum F)

Adsorption

Adsorption of bitter tasting drug can be considered as the less saliva soluble versions of these drugs. Adsorption involves preparing a solution of the drug

and mixing it with an insoluble powder that will absorb the drug, removing the solvent, is dried and used in the preparation of the final dosage form. Many substrates like veegum, bentonite, silica gel and silicates can be used for the preparation of adsorbate of bitter drugs.

Prodrug approach

Chemical modification, including prodrug design is an effective method for reducing solubility, and improving taste. A prodrug is chemically modified inert drug precursor which upon biotransformation liberates the pharmaceutically active parent compound. Bitterness of a molecule may be due to the efficiency of the taste receptor substrate adsorption reaction, which is related to the molecular geometry of the substrate. If alteration of the parent molecule occurs by derivative formation, the geometry is altered, affecting the adsorption constant. Thus the magnitude of a bitter taste response or taste receptor-substrate adsorption constant may be modified by changing the molecular configuration of the parent molecule. The extremely bitter antibiotics have been the focus of much work in reversible drug modification (table no. 6).

Table 6. Prodrug for bitter taste masking

Parent molecule	Reversible modification
Chloramphenicol	Palmitate or phosphite ester
Clindamycin	Alkyl ester
Erythromycin	Alkyl ester
Lincomycin	Phosphate or alkyl ester
Tetracyclin	3,4,5-Trimethoxy benzoate salts

Solid dispersion system

Solid dispersion have 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, mannitol and ethyl cellulose

Various approaches for prepration of solid dispersion are described below.

i) 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 & pulverised.

ii) 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.

iii) 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.

Multiple emulsion technique

Multiple emulsions are complex poly dispersed systems having oil in water and water in oil emulsion simultaneously existence, stabilized by lipophillic and hydrophilic surfactants respectively, prepared by dissolution of drug in inner aqueous phase of w/o/w emulsion under good shelf stability condition. This technique successfully utilizes in masking the bitter taste of chloroquine (broad-spectrum antimalarial drug) [12].

Miscellaneous

a) By effervescent agents

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have 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 was formulated to supply the medicament to oral cavity for local application or for buccal absorption. It comprise a chewing base, an orally administrable medicament, a taste masking generator of carbon dioxide, and optionally a taste bud desensitizing composition (eg, oral anaesthetic such as benzocaine) and other non active material such as sweeteners, flavoring components, and fillers. Recently, effervescent tablets of fentanyl and prochlorperazine were developed to supply these drugs to the oral cavity for buccal, sublingual, and gingival absorption. The formulation contain the drug in combination with effervescent agent to promote their absorption in the oral cavity and to mask their bitter taste. An additional pH adjusting substance was also included in fentanyl formulation for further promotion for absorption.

b) 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. 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 unpleasent taste of the drug, it also inhibit its undesirable local anaesthetic effect.

c)Continuous multipurpose melt (CMT) Technology

The CMT method was developed for the continuous granulation and coating of pharmacologicly active substances. It was concluded that this method could be succesfully applied for taste masking of bitter drugs [7].

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 measures 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 (eg. 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 drugs 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.

Measurement of Frog Taste Nerve Responses

In this method, adult bull frogs are anaesthetized intraperitoneally and the glossopharyngeal nerve is then located and dissected from the surrounding tissue and cut proximally. 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 byPA-LG(phosphatidicacid-lactoglobulin)combination have been reported to be evaluated by this technique.

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. 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 them 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.

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 [13].

Recent Trends

AdvaTab ODT Technology

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

Microcaps ODT Technology

Microcaps 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 odour. Offers 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 temperature with non organic solvent.

KLEPTOSE® Linecaps

Roquette offers a new taste-masking technology: KLEPTOSE® Linecap uses a pea maltodextrin for masking the bitter taste of drugs by decreasing the overall amount of drug particles exposed to the taste buds [14].

Conclusion

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 is 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 the treatment 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.

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