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"MASKING OF TASTE OF PHARMACEUTICALS - A CURRENT REVIEW ON USEFUL TECHNOLOGIES"

Pharmaceutical Science

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ABSTRACT

The problem of bitter and obnoxious taste of drug in pediatric and geriatric formulations is a challenge to the pharmaceutical industry in the present scenario. Taste is an important factor in the development of dosage form and it is that parameter of product development which has been curiously studied and developed by the researcher for its importance. Taste masking technologies offer a great scope for invention and patents. Taste masking ensure better patient compliance for bitter or objectionable taste of drugs formulations as this desirable aspect will provides commercial gains to pharmaceutical industries due to higher market demand of products, patent protection to novel taste masked formulations and also for exclusive marketing rights. The logical objective of present review is to explore and compile different method, technologies for specific dosage forms and evaluations techniques of taste masking the obnoxious taste of drugs for better patient suitability.

KEYWORDS

Masking, Pharmaceutical, Taste, Technologies, Bitter, Flavours, Sweeteners

INTRODUCTION

Taste is arguably the only external sense an essential required important parameter of oral pharmaceuticals which can provide better patient compliance. While undesirable taste of several formulation presents problems, which is encountered with certain natural as well as synthetic drugs and constraints the impact of oral administration frequently encountered by health care providers, especially in case of pediatric - geriatrics patients. [1] It is well known that people live in our societies without sight, hearing or smell. Even some somatosensory and proprioceptive deficits are overcome with visual feedback, but people without taste often do not eat and without medical intervention would die. [2] Molecule interacts with taste receptor on the tongue to give bitter, sweet or other taste sensation, when they dissolve in saliva. Taste is the main sensory modality by which we evaluate a potential food is friend or foe. Taste of drug and drug product is an important parameter as it directly relates to the patient acceptability, compliance, and prescribing practice of various oral formulation.[3] Most medicines have objectionable, particularly bitter taste. Quite often, a drug formulation has to be designed in a manner wherein the preparation is either a liquid or solid but oral or orodispersible, intended for pediatric patients or geriatric patients having difficulty in swallowing of undesired taste. Masking of bitter or objectionable taste of such formulations is highly desirable which provides commercial gains to pharmaceutical industries due to higher market demand of products, patent protection to novel taste masked formulations and also in some cases extended marketing exclusivity rights.

Physiology of Taste

Taste buds on the tongue are onion-shaped structures containing between 50 to 100 taste cells.[4] Chemicals from food or oral ingested medicaments are dissolved by the saliva and enter via the taste bud pores. There they either interact with 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 for taste perception.

Taste Sensations

Sensing of foods by the taste system has been critical for species survival, signaling via taste quality whether the food is fit for ingestion. There are four well established basic tastes: sweet, sour, salty, and bitter; all with perceptual independence, salience, and hedonic responses to encourage or discourage consumption.[5][6]

Sweet–
indicates energy rich nutrients. Sweet taste is due to polyhydroxy compounds, polyhalogenated aliphatic compounds and alpha-amino acids. Imides such as saccharin are intensely sweet.

Salty –
Saltiness is due to simultaneous presence of anions and cations, e.g. Potassium Bromide, sodium salicylate and high molecular weight salts may have a bitter taste.

Sour–
taste of acids, modulates pH. It is due to the presence of hydrogen ions and is characteristics of acids, phenols, lactones, etc.

Bitter-
allows sensing of diverse natural toxins. Free bases such as alkaloids and amides such as amphetamines give bitter taste.

All of these tastes are elicited and perceived by not only a single chemical but variety of chemical constituents present in food items. There are thresholds for detection of taste that differ among chemicals that taste the same. For any chemical entity to elicit taste response has to overshoot the response over its threshold level. ***Table 1*** depicts the human threshold for taste for different chemical substances.

Table 1: Examples of human thresholds for various substances and their taste

Taste	Substance	Threshold for Tasting
Salty	Sodium chloride	0.01M
Sour	Hydrochloric acid	0.0009M
Sweet	Sucrose	0.01M
Bitter	Quinine	0.000008M

Factors affecting Tate Masking:

Factors that are taken into consideration during the taste-masking formulation include various physical and chemical properties of active pharmaceutical ingredients like Extent of the bitter taste of the API, required dosage form, drug particulate shape and size distribution, Drug solubility and ionic characteristics, required disintegration and dissolution rate of the finished product, Desired bioavailability, Desired drug release profile etc. [7][8]

Taste Masking Technologies:

Taste masking is defined as perceived reduction of an undesirable taste that would otherwise exist. Taste masking technologies offer a great scope for invention and patents making suitable medicinal preparation with palatability. Use of additives like sweeteners of flavors, use of lipoproteins for inhibiting bitterness, numbing of taste buds, viscosity modifiers, prodrug formation, salt formation, formation or inclusion and molecular complexes, solid dispersion system and application of

ion exchange resins have been tried to mask the unpleasant taste of the bitter drugs. Other technologic intervention includes applying coating layers, microencapsulation or even chemical modification have been employed to improve taste compliance. [9] This review endeavours to present the practical technologies and platforms applied for taste masking with respect to dosage form and indicate the interesting features of each approach.

The most widely adopted method for masking bitterness of drug or drug product by various means which can be broadly divided into 3 categories-

A. Physiological methods
B. Physical methods
C. Chemical methods

A. Physiological or Psychological Modulation of Bitter Taste and Taste Overshadow:

Taste modulation and overshadow are the simplest and easiest approaches to overcome bitterness of drug. This can be achieved in any one of the following ways:

1. Use of cooling compounds and local anaesthetics:

Natural cooling agents such as menthol, menthone, methyl acetate and peppermint oil while local anaesthetics such as lidocaine can prevent perception of bitterness and reduce the intensity of bitterness. [10]

2. Use of high intensity sweeteners:

Sweeteners are very commonly used additive to mask drug bitterness. Each sweetener will have their own significance in taste masking and different value of sweetness when compared to standard Sucrose. [11]

Though it is fact that complete masking of objectionable taste with sweeteners may not be possible in all situations but sweeteners are added to bitter drug formulations to increase their palatability. ***Table 2*** lists some of the high intensity sweeteners and their relative intensity of sweetness compared to sugar. [12]

Table 2: Sweeteners with High intensities and their relative intensity of sweetness

Sweetener	Sweetness in relation to sucrose	Significance
Glycyrrihizine	50-100	Moderately expensive
Aspartame	180	Less stable in solution
Acesulfame potassium	200	Bitter in higher concentration
Saccharin sodium	300	Unpleasant after taste
Stevioside	300	Low-Calorie Dietary Replacement
Sucralose	600	Synergestic sweetening effect
Hernandulcin	1000	Low caloric potential
Monellin	1500-2000	Water soluble protein for Sweetening Foods and Drinks
Neohesperidine dihydrochalcone	1800	A Xenobiotic
Alitame	2000	Excellent stability at high temperatures.
Thaumation	2000-3000	A taste-modifying protein that functions as natural sweetener or flavor enhancer.
Neotame	8000	High degree of Sweetness
Lactose	0.16	High amount is required
Mannitol	0.60	Negative heat of solution

3. Use of flavors:

Flavors are known to accentuate the sweetness of the formulation while aiding dominance over bitter taste perception and hence play very important role in masking the objectionable taste of medicaments. Flavours are classified into natural and artificial and selection of suitable flavouring agent to be added depends on the original sensation of drug substance. [13],[14],[15] The flavors used for taste masking purposes have often been classified depending upon the basic taste that is to be masked.(see ***Table 3***). [16]

Table 3: Basic Taste and Masking Agents Used.

Basic Taste	Masking agents
Sweet	Vanilla, bubble gum, grapefruit
Acid	Lemon, lime, orange, cherry, grapefruit
Metallic	Grape, marsh, mellow, guarana, berries, mints
Bitter	Liquorice, coffee, chocolate, mint grapefruit

Selection of suitable flavouring agent to be added depends on the original sensation of drug substance. Examples of various classes of drugs of which the taste masking is achieved by the use of sweeteners and flavouring agents are listed in below ***table 4***: [17],[18]

Table 4: Example of drug substances and their taste masking agents.

Drug	Category	Dosage form	Taste	Taste masking agent used
Eucalyptus oil	Freshener	Mouth wash, Ointments, Dentifrices	Bitter	Fenchone, Borneol
Ibuprofen	NSAID	Syrup, Suspension	Bitter	Saccharin sodium, sucrose, sorbitol
Thymol, triclosan	Dental caries	Oral rinses	Bitter	Citrus flavour, limonene
Zinc acetate dehydrate	Zinc supplement	Lozenges	Bitter	Saccharin sodium
Amino acids and proteins	Diet supplement		bitter, salty/ sour.	Sucralose
Levofloxacin	Fluoroquinolone antibiotic	Tablet	Metallic	Aspartame, Sucralose, Saccharin sodium
Aspirin / Acetaminophen	NSAID	Tablet, Syrup, Suspension	Bitter	Menthol, Aspartame / Sucralose, Citric Acid
Iron compounds	Iron supplement	Syrup	Metallic	Sucralose, sorbitol, Xylitol, Maltitol or Erythritol
Guaifenesin and Dextromethorphan hydrobromide	Expectorant	Syrup	Bitter	Sucralose, Citric acid

4. Blocking of taste receptors:

Bitter taste is mediated by G protein-coupled receptors of the taste receptor 2 family (gene symbol: TAS2R or Tas2r in rodents) but there are number of TAS2R genes differs considerably among vertebrates, ranging from 3 in chicken to 49 in frog. [19] Naturally occurring compounds such as gymnemic acid decreases the sweet perception by competitive inhibition of the sweet receptor.[20] Artichokes have the opposite effect, enhancing sweet taste by suppression of sour and bitter taste receptors.[21] Miracle fruit turns sour tastes sweet.

The active ingredient, “miraculin”, binds to a site near the sweet receptor.[22] When sour substances are tasted subsequently, a conformational change in the taste cell membrane occurs in such a way as to bring the miraculin molecule into contact with the sweet receptor, activating it.[23] Amiloride, a blocker of epithelial sodium channels, reduces salt taste in humans and adenosine monophosphate (AMP) may block the bitterness of several bitter tasting agents.[24]

B. Physical Methods of Taste Masking

The various physical methods of taste masking include –

1. Physical barrier approach:

This concept is attributed to involvement of certain pharmaceutical technologies such as coating, microencapsulation, emulsification, and liposome formation.[25] Exhaustive studies of various parameters of taste physiology and drug property for selected dosage form are utilized before employment of any method to mask the taste. Some of these methods are:

a) Coating with saliva insoluble materials:
A physical barrier coated onto the active ingredient could successfully provide a palatable oral dosage form, as the coating prevents early dissolution of drug in the mouth. [26] Several water insoluble polymers and waxes can be used for achieving this objective. Prominent among these materials include ethy1cellulose, Eudragit E100, Eudragit L100, cety1 alcohol, stearic acid, glyceryl monostearate, etc. Generally, drug crystals, granules or pellets are coated with such materials to affect taste masking. [27] Fluidized bed coating technology is a commonly used approach to apply a continuous coat around the core particle. Generally, there are two types of techniques that can be applied when using fluidized bed coating technology, the first one is Coating using a polymeric solution and the second is Coating using molten materials such as waxes. [28],[29],[30],[31]

b) Coacervation/phase separation:
Coacervation is one of the most easily applied technology for the formation of polysaccharide-based delivery systems. It is a process that involves phase-separation to form two separate liquid phases consisting of a polymer-rich phase and polymer-depleted phase. [32]

Though coating here done of drug particles is in fluid-bed processor is also microencapsulation technique, classic microencapsulation methods have been used to mask bitterness of drugs with various polymers. [33], [34], [35], [36], [37], [38], [39] For example, Microcaps [R](Eurand) is a well-recognized coacervation/phase separation technology used to encapsulate drug substances. [40],[41],[42]

c) Supercritical fluids (SCFs) technique:
A rather limited approach for taste masking is the use of supercritical fluids (SCFs) a one-step process.[43], [44] The unique property of supercritical fluids, in particular supercritical carbon dioxide (CO_2), provide numerous opportunities for the development of processes for pharmaceutical applications. [45] The drug and the polymers are dissolved in organic solvent and then sprayed into a high-pressure chamber filled with supercritical carbon dioxide. SCF technology has been successfully applied to provide a fluffy, taste-masked aspartame powder coated with ethyl cellulose. [43]

d) Vapour deposition process:
Chemical Vapour Deposition (CVD) of films and coatings involve the chemical reactions of gaseous reactants on or near the vicinity of a heated substrate surface. This atomistic deposition method can provide highly pure materials with structural control at atomic or nanometer scale level.[46] This technique can be used to coat drug with polymers such as poly-p-xylene parylene C. [47], [48] In this method, Parylene C is vaporized at a temperature above 170 ^{0}C, followed by pyrolysis of the vapours at around 690 ^{0}C to form the gaseous reactive monomer para-xylene. This reactive monomer is deposited onto the drug particle. The drug particle, which has a lower temperature, causes the reactive monomer to condense on the surface of the drug particle and polymerise. [26]

e) Spray drying:
This technique enables the transformation of feed from a fluid state into dried particulate form by spraying the feed into a hot drying medium. It is a continuous particle processing drying operation in which the feed can be a solution, suspension, dispersion or emulsion. [49] Spray drying can be used to produce either microcapsules or microspheres in which drugs are coated with polymer dissolved or dispersed in a polymer matrix, respectively. The type of microparticle obtained was found to be dependent upon the solubility of drug in the coating material. Microspheres are produced by spray drying the coating solutions in which the drug is soluble. If the drug is insoluble in the coating solution, microcapsules are produced.[50]

f) Spray congealing:
Spray congealing is a low cost, simple and versatile method to produce microparticles or microcapsules without the use of organic or aqueous solvent. [51] High encapsulation efficiency, spherical shaped particles with CR properties can be obtained by using the appropriate type and amount of meltable material. Spray congealing may not be suitable for hydrophilic drugs such as verapamil because of the poor encapsulation rate. This problem may be tackled by using a more hydrophilic wax such as stearyl alcohol and/or a surfactant such as soya lecithin. [52]

g) Emulsification method:
Simple emulsions, multiple emulsions or microemulsions can be used to effectively mask the bitterness of several drugs. [53] In case of simple emulsions, the bitter water-soluble drug is incorporated in water that is used as the internal phase and then emulsified in edible oil as the external phase that is bland. [54] A more palatable form of emulsion is formulation of multiple emulsion such as w/o/w where in the bitter drug is incorporated in the innermost aqueous phase or in the sandwiched oil phase. [55] The external phase contains organoleptic agents such as sweeteners and flavors.

h) Liposomes:
Liposomal act as drug delivery systems which has profound biodistribution of their associated drugs by delaying drug clearance, retarding drug metabolism, decreasing the volume of distribution, and shifting the distribution in accordance of diseased tissues with increased capillary permeability. This increases the therapeutic indices of the associated drugs, by increasing the drug concentration in solid tumours and regions of infection, and reducing the drug concentration in normal tissues. Three liposomal formulations have been approved for clinical use. [56] This technique of masking the unpleasant taste of therapeutic agent is to entrap them into liposome. For example, incorporating into a liposomal formulation prepared with egg phosphatidyl choline masked the bitter taste of chloroquine phosphate in HEPES (N-2- hydroxyetylpiperzine-N'- 2- ethane sulfonic acid) buffer at pH 7.2. [1]

2. Densification method:
In this method, fine drug particles that may otherwise dissolve readily in saliva and give bitter taste are densified and converted in relatively larger particles having lesser surface area for dissolution in saliva owing to which they exhibit lesser degree of bitterness. [57] Furthermore, such densified particles are easy to coat as compared to fine drug particles with polymer in order to completely mask the objectionable taste of the medicament. [58] Dense and slowly soluble compact masses can be prepared by techniques such as that granulation or extrusion. [59] This technique can be used more effectively to mask drug bitterness by employing water insoluble binders or polymers such as ethyl cellulose, enteric polymers like hypromellose phthalate (wet granulation) or hydrophobic waxes such as stearic acid (melt granulation).

3. Adsorption method:
Adsorption is the process in which materials of one phase accumulate or concentrate at the interfacial surface of the other phase. It occurs at the interface of two phases such as liquid/liquid, gas/solid, gas/liquid, or liquid/solid. [60] Three different types of adsorption processes exist viz *a) Lipophobicity of the solute against the solvent, b) Physical adsorption (physisorption), c) Chemical adsorption (chemisorption)*. However, most adsorption processes are dominated by a combination of all three types of adsorption.[61]Certain magnesium compounds such as magnesium oxide, magnesium carbonate and magnesium aluminum silicate have tremendous capacity to form adsorbates especially with basic drugs. Adsorption of various drugs onto magnesium oxide has been reported, such as antihistamines, antibiotics (especially tetracyclines), salicylates, atropine sulphate, hyoscyamine hydrobromide, paracetamol, chloroquine and anthranilic acid derivatives have been reported to adsorb onto the surface of magnesium oxide. [60],[62],[62],[64],[65],[66],[67]Magnesium aluminum silicate, as with other clays, may adsorb some drugs.[68],[69]

C. Chemical Methods of Taste Masking
Chemical methods basically include the converting of unpleasant drug in to modified chemical form which can be referred as prodrug which have altered solubility, and thereby improving taste with inert drug precursor which upon biotransformation liberates the pharmaceutically active parent compound.[70] The two chemical modification approaches include-

1) Complexation method:
This method involves formation of weak chemical complexes between drug and the complexing which dissociate in GI milieu. Various Complexation techniques employed for taste masking are elicited below.

a) Complexation with ion-exchange resin:
Ion-exchange resins are high molecular weight polymers with cationic and anionic functional groups. The drug can be bound to the resin via an oppositely charged resin substrate, forming insoluble adsorbates or resinates so that dissociation of the drug-resin complex does not occur under the salivary pH conditions. In this way, strong taste-masking

properties can be achieved to minimize the unpleasant taste and odour of drugs.[69] Ion exchange resins (IER) have versatile properties as drug delivery vehicles. [71] Polystyrene matrix cation-exchange resins (Indion 204, Indion 214, Indion 234) have been reported to mask the bitter taste of norfloxacin, ofloxacin, ciprofloxacin and chloroquine phosphate.[72] Amberlite IRP-69, IRP-64 is a strongly acidic, sodium from cation-exchange resin used to mask the bitter taste of buflomedil.[73] Resins have also been found to be applicable to consumable solid films, example Kyron T-114 and Kyron T-104 where bitter drug agents are adsorbed to the ion-exchange resin.[74]

b) Inclusion Complexation with cyclodextrins:

Cyclodextrins are most commonly used complexing agents. [75],[76]They mask the taste of bitter drugs by either decreasing its oral solubility or decreasing the amount of drug particles exposed to the taste buds. [77],[78] Cyclodextrins with lipophilic inner cavities and hydrophilic outer surfaces are capable of interacting with a large variety of molecules to form non-covalent inclusion complexes.[79] A well know multiplatform for taste-masking purposes is Captisol ® (CyDex, Inc.) a Polyanionic β-cyclodextrin derivative.[80],[81] Its main advantage is neutral, cationic and anionic drugs can be effectively complexed by Captisol. The drug complex can be isolated using lyophilization, spray drying or by application onto another substrate.

a) Complexation with tannic acid:

Tannic acid is known to complex with several amine containing drugs and the resulting complex act both as taste masked derivative as well as sustained release form Antihistamine tannates that exhibit both these properties are prepared by simple Complexation of drug with tannic acid in water or a suitable solvent.[82]

2. Prodrug formation:

A Prodrug is a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent drug.[83] Prodrug are generally ester form of drugs having poor aqueous solubility. Examples of drug with improved taste are given in ***table 5***.[84]

Table 5: Prodrug with improved taste.

S.no.	Parent drug	Prodrug with improved taste
1	Chloramphenicol	Palmitate ester
2	Clindamycin	Palmitate ester
3	Triamcinolone	Diacetate ester
4	Propoxyphene	Napsylate ester
5	Erythromycin	Ethyl succinate ester

3) By effervescent formation:

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. [85], [86] The zinc salt of bacitracin has low aqueous solubility and thus much reduced bitterness similarly, magnesium salt of omeprazole is water insoluble, more stable and less bitter and can be easily formulated as chewable buffered tablets. [87]

4) Alteration of pH:

Modification of microenvironment pH of solid dosage form of a bitter drug or pH of liquid oral formulation that prevents solubilization of drug in saliva or in aqueous fluids, can be successfully employed to mask bitter taste of majority of drugs. [26] For example, maintaining alkaline pH for basic drugs prevents their dissolution in saliva and thus taste perception. [88]

Evaluation of Taste Masking Effects

As taste is subjective perception, highly depend on the individual to individual who perceives the taste and it may vary to different degree. There is some direct method for taste evaluation by a trained flavour profile panel and controlled experimental models that can ascertain the degree of masked taste accurately upto possibilities threshold of pharmaceuticals with reference to standard taste. [89]

Taste analyzing sensors have also been developed for similar purpose. To quantitatively evaluate taste sensation, following methods have been reported in Literature. [90],[91],[92]

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

CONCLUSION:

Taste masking of bitter-obnoxious drugs has significantly improved the quality of treatment to suffering patients especially children and geriatrics. There are many effective technologies and methodologies to mask the taste of active drug compounds and are constantly being researched and developed in the pharmaceutical field in response to the need. Application, suitability and acceptance of all these approaches varies from drug to drug and dosage form. The identified need to bitterness reduction or inhibition is the discovery of a universal inhibitor of all bitter-tasting substances that does not affect the other taste modalities such as sweetness. But to date there is no single substance that acts as the universal inhibitor of a bitter taste. Research for the same has been performed for a long time. With application of these techniques and proper evaluation of taste masking effect one can improve product preference to a large extent. Further research on taste masking should focus on substances of a natural origin to permit their commercial use in improving the palatability of oral pharmaceuticals.

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