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A REVIEW: MASKING OF TASTE UNIQUE APPROACHES FOR BITTER DRUG

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ABSTRACT

More than 50% of pharmaceutical products are orally administered for several Reasons and undesirable taste is one of the important formulation problems that is Encountered with such oral products. Taste of a pharmaceutical product is an important parameter governing compliance. Hence taste masking of oral Pharmaceuticals has become important tool to improve patient compliance and the Quality of treatment especially in paediatrics. Different methods have been suggested for Masking of taste of bitter drugs, which includes, coating of drug particles with inert agents, taste masking by formation of inclusion complexes, molecular complexes of drug with other chemicals, solid dispersion system, microencapsulation, multiple emulsions, using liposome's, Prodrugs and mass extrusion method but ion exchange resin is one of most extensively Used method to overcome this problem. Ion-exchange resins (IER) have received considerable attention from pharmaceutical scientists because of their versatile properties as drug-delivery vehicles.

KEYWORD: Taste, taste masking, oral pharmaceuticals, Bitter drugs, Ion exchange resin, Taste masking technology

INTRODUCTION

Definition

Is defined as apperceived reduction of on undesirable taste that would otherwise exist. the ideal solution to reduce or inhibit bitterness is the discovery of a universal inhibitor of all bitter testing substance that does not affect the other taste modalities such as sweetness or saltiness.

The sense of taste

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

Human have around 10,000 taste buds which appear in foetus at about three months. A single taste bud contain 50-100 taste cells. These are Trans membrane proteins which bind to the molecules and ions that give rise to the four primary taste sensations namely- salty, sour, sweet and bitter taste buds. Recently, a fifth basic taste umami has been discovered. The umami is the taste of certain amino acids. There is often correlation between the chemical structure of compound and its taste. Low molecular weight salts tend to taste salty where as high molecular weight salts tend toward bitterness. Nitrogen containing compounds, such as alkaloids, tend to be quite bitter. Organic compounds containing hydroxyl groups tend to become increasingly sweet as number of OH group increases Receptor mechanism involves initial depolarization at apical receptor site, which causes local action potential in receptor cell. This in turn causes synaptic activation of the primary sensory neuron.

Taste Masking Techniques

1. Addition of flavouring and sweetening agents.
2. Microencapsulation.
3. Ion exchange resins.
4. Inclusion complexes.
5. Granulation.
6. Adsorption.
7. Prodrug approach.
8. Bitterness inhibitors.
9. Multiple emulsions.
10. Solid dispersion.
11. Molecular complexes.
12. Gel formation.
13. Use of liposomes.
14. Mass extrusion method.
15. Use of salt and derivative.

16. Use of amino acids and protein hydrates.
17. Miscellaneous

1) Addition of flavouring and sweetening agents

This techniques is simplest approach for taste masking. But this approach is not very successful for these taste masking agents significantly suppress the perception of unpleasant organoleptic sensations of the volatile oil. The cooling effect of the taste masking agents also aids in reducing the bitterness highly bitter drugs.

- **Natural flavours**

Juices- raspberry, Extract- Liquorices, Tinctures-Ginger, Spirits-Lemon & Orange Syrup-Blackcurrant

Aromatic water-Anise & Cinnamon, Aromatic oil-Peppermint & Lemon.

- **Synthetic Flavours**- Alcoholic solution, aqueous solutions, Powder.
- **Sweetener**

- Natural –Sucrose, Glucose, Fructose, Sorbitol, Mannitol, Honey, Glycerol, Liquorice
- Artificial- Saccharin, Saccharin sodium, Aspartame
- Nutritive-Sucrose, Fructose, Glucose
- Non-Nutritive-Aspartam, Sucralose, Neotame, Saccharine
- Polyols- Mannitol, Sorbitol, Xylitol, Erythritol Maltitol
- Novel-Trehalose, Tagatose

Table 1: Flavouring and Sweetening.

Drug	Flavour ant /Sweetener
Ampicillin	Glycine
Cetirizine Dihydrochloride	Grape, vanilla
Cetirizine Hydrochloride	Aspartame, Sucralose, Lemon Flavour, Citric acid

2) Microencapsulation

Microencapsulation is a process by which very tiny droplets or particles of liquid or solid material are surrounded or coated with film or polymeric material. It is important to understand that only soluble portion of 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 and 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.

The goal of microencapsulation may be accomplished by any of following techniques:

1. Air suspension coating.
2. Coacervation phase separation.
3. Spray drying and spray congealing.
4. Solvent evaporation.
5. Multiorifice-centrifugal process.
6. Pan coating.
7. Interfacial polymerization

Thin coating to small particle of solids, droplets of liquid and dispersion.in these techniques general used coating agent are following-

- Gelatine, povidone, Hydroxyethyl cellulose, ethyl cellulose, bees wax, carnauba wax shellac.
- Water insoluble polymer-cellulose ether, cellulose ester, polyvinyl acetate.
- Water soluble polymer-cellulose acetate butyrate,PVP Hydroxyethyl cellulose's

Table no: 2: Microencapsulation.

Chloroquine diphosphate	Vinyl pyridine
Beclamide	Gelatine
Diphenhydramine (DPH)	Starch
Acetaminophen	Eudragits
Pseudoephedrine hydrochloride	Ethyl cellulose ,cellulose acetate
Diclofenac sodium	Ethyl cellulose
Ofloxacin	Eudragit E100

3) Ion Exchange Resin

One of the popular approaches in the taste masking of bitter drug is based on IER. IER are solid and suitably insoluble High Molecular weight Polyelectrolytes that can exchange their mobile ion of Equal charge with the surrounding Medium.

For Taste Masking Purpose are Weak Cation Exchange resins are used depending on the Nature of drug. The Nature of drug resin complex formed in such that the average pH of 6.7 & cation Concentrate of about 40 meq/c in the saliva are not able to break the drug resin complex but it is weak enough to break down by HCL present in the stomach. Thus the drug resin complex is absolutely tasteless with no after taste and at the same time, its bioavailability is not affected.

Classification

IERs Contain positively or negatively charged sites and are accordingly classified as either cation or anion exchanger.

- Strong cation exchanger- Sulphuric acid sites
- Weak cation exchanger- Carboxylic acid.
- Strong anion exchanger-quaternary amine ionic sites
- Weak anion exchanger- tertiary amine substituents.

E.g. Indion 204, 234, 244, 254, Tulsion T-335 T-339

T-334 Amberlite Irc 50, IRP69, IRP 88, IR120 Dowex 50.

Mechanism of Binding of Ion Exchange Resin with Drugs

The principle property of resins is their capacity to exchange bound or insoluble ions with those in solution. Soluble ions may be removed from solution through exchange with the counter ions adsorbed on the resin as illustrated in equation 1 and 2.

Re-So3 – Na+ + Drug+ Re-SO3 – Drug+ + Na+

……..1

Re-N (CH3) + Cl– + Drug – Re-N (CH3) + Drug – +Cl-

……2.

These exchanges are equilibrium reactions in which the extent of exchange is governed by the relative affinity of the resins for particular ions.

Table 3: Ion Exchange Resins.

Azithromycin	Dowex, indion 234, indion 214
Amphetamine	AmberliteIPR69
Amodiaquine HCL	KyronT134
Chloroquine phosphate	Polyacrylic acid, amberlite IPR88
Ciprofloxacin	Tulsion T339, Indion 234, indion294
Clarithromycin	Carbomer934
Cefuroxime axetil	Kyron T 104
Dicyclomine HCL	Amberlite IR120, Dowex 50, Kyron T154, INdion 214, indion 244
Dimenhydrinate	AmberliteIPR 50, Indion 204
Doniperil chloride	Amberlite IPR64
Diphenyhydramine	Indion 234, Tulsion 343, Indion CPR 244
Erythromycin	Carbomer
Paracetamol	Tulsion 339
Ofloxacin	Tulsion T335, Kyron T114
Propranolol HCL	Tulsion
Quinine	Dowex
Ranitidine HCL	Amberlite IPR88, Amberlite IPR69

4) Inclusion Complexes

Inclusion complexes are 'host-guest' relationship in which complexing agent act as host and provide cavities in which foreign guest molecules may fit.

Cyclodextrin form inclusion types of complexes with organic molecules both solid state and in solution.

The complexing agent is capable of masking bitter taste of drug by either decreasing its oral solubility on ingestion or decreasing amount of drug particles exposed to taste buds, thereby reducing the perception of bitter taste. Vender wall forces involved in inclusion complexes.

Cyclodextrin is most widely used complexing agent for used complexing agent for inclusion type's complexes. It is sweet, nontoxic cyclic oligosaccharides obtained from starch. The Taste of the guest drug masked by 2 approaches.

- By decreasing its oral solubility in ingestion.
- By decreasing the amount of drug particle exposed to taste buds reducing the perception of bitter taste.

The suppression of bitter taste by cyclodextrin was increases in increasing order of alpha, gamma, and beta cyclodextrin.

Table 4: Inclusion Complexes.

Dextromethorphan	Cyclodextrin
Cholroquine phosphate	Tannic acid
Ibuprofen	Hydroxypropyl B-cyclodextrin
Metronidazole benzoate	Alpha cyclodextrin
Zipeprol	B-cyclodextrin
Hexitidine	B-cyclodextrin
Famotidine	HPMC
Cefuroxicam	Beta –cyclodextrin

5) Taste Masking by Granulation

Granulation is a common processing step in the production of tablet dosage form. This step can be exploited as a mean for taste masking of slightly bitter tasting drug. Some saliva insoluble polymers can also act as binding agent, granules prepared from these polymers show less solubility in saliva and thus taste could be masked. Granulation lowers the effective surface area of the bitter substance that comes in contact with the tongue upon oral intake. But this reduction in surface area of bitter substance may or may not be effective in masking

the bad taste. Taste masked granules, prepared from saliva insoluble polymer, can be formulated in various type of tablet dosage form. Example rapidly disintegrating tablets and chewable tablets.

Table no 5: - Granulation.

Erythromycin	Alginic acid
Dextromethophan	Cyclodextrin
Ibuprofen	Microcrystalline cellulose

6) Taste Masking by Adsorption

Adsorbate 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 adsorb the drug, removing the solvent, drying the resultant powder, and then using these dried adsorbates in the preparation of final dosage form. Many substance like veegum, bentonite, silica gel and silicates can be used for the preparation of adsorbate of bitter drugs. Loperamide and phenyl propanolamine have been adsorbed on magnesium aluminium silicates also known as veegum F to prepare bitter taste masked suspension of these drugs.

Table no 6:-Adsorption.

Loparamide	Magnesium aluminium silicates
Phenyl propanolamine	Magnesium aluminium silicates
Ranitidine	Magnesium trisilicate
Dextromethoprim	Magnesium trislicate

7) Prodrug

Prodrug is defined as therapeutics agents that are inactive moieties but on biotransformation liberate the pharmaceutically active parent metabolites. By changing configuration of the parent molecule the magnitude of a bitter taste response or taste receptor-substrate absorption constant may be modified. Prodrug can be used to increase or decrease the aqueous solubility, mask bitterness, increase lipophilicity, improve absorption, decrease local side effect, and alter membrane permeability of the parent molecules.

Table 7: Prodrug for bitter taste masking.

Parent molecules	Reversible modification
Chloramphenicol	Palmitate or hydrochloride ester
Clindamycin	Alkyl ester
Erythromycin	Alkyl ester
Lincomycin	Hydrochloride or alkyl ester
Tetracycline	3,4,5trimethoxy benzoate salts

8) Taste masked by bitterness inhibitor

The development of a specific universal inhibitor for bitter taste has been widely required in the fields of taste physiology and pharmaceutical sciences, but no such inhibitors has been available.

One difficulty in discovering of universal inhibitor for bitter taste is that substances that inhib its bitterness of one compound will not influence the bitterness of a second because many different classes of compound impart bitterness. Sodium salts such as sodium chloride, sodium acetate, and sodiumgluconate have been shown to be potent inhibitors of some bitter compounds. The mechanism is not known however research shows that sodium act at peripheral taste level rather than a cognitive effect.

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9) 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 Providence, Polyethylene Glycol of various molecular weights, Hydroxyl Propyl Methyl Cellulose, Urea, Mannitol and Ethyl Cellulose. Various approaches for preparation of solid dispersion are described below:

Table No 8: - Solid dispersion System for bitter taste masking.

Acetaminophen	Polyethylene glycol(PEG)
Ketoprofen	Eudragit RS
Trypsinogen	Lipid tripalmitin(TP)
Verapamil	Methacrylic acid &copolymer eudragit
Dimenhydinate	Polyvinyl acetate ahthalate

9.1 Melting Method

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

9.2. 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.

9.3. Melting Solvent Method

In this method, drug in solution is incorporated into molten mass of polyethylene glycol at a temperature 700C without removing the solvent.

10) Taste masking By Multiple Emulsion

A novel techniques for the taste masking of drugs employing multiple emulsion has been prepared by dissolving drug in the inner aqueous phase of w/o/w emulsion under the conditions of good shelf stability. The w/o/w or o/w/o type multiple emulsion are vesicular systems in which active ingredients can be entrapped in internal phase. The entrapped substances can be transferred from internal phase to external phase through the membrane phase. This phase controls the release of drug from system. This system could be used for controlled-release delivery of pharmaceuticals.

Table No 9: Multiple Emulsion for Test Masking.

Drug	**Polymer**
Polylactic acid	Nacl, Cacl2, brilliant blue dye.

11) Molecular Complexes

The solubility and adsorption of drug can be modified by formation of molecular complexes. The intensity of bitterness by modifying the solubility and absorption of drug in the formation of complex. This usually decrease the intensity of bitterness of drug. Higuchi and pitman

reported that caffeine forms complexes with organic acid that are less soluble than xanthene sand as such as can be used to decrease the bitter taste of caffeine.

12) Gel Formation

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

13) Use of Liposomes

Another way of masking the unpleasant taste of therapeutics agent is to entrap them into liposome. For example, incorporating into a liposomal formulation prepared with egg phosphotydyl choline masked the bitter taste of Ofloxacin Hydrochloride in HEPES (N-2-Hydroxyethylpiperazine-N‟-2)-ethane sulfonic acid) buffer at pH 7.2.[90] Bitter substances are commonly hydrophobic in nature hence lipoprotein composed of phosphatidic acid and β-lactoglobulin can mask the target sites for bitter substances on the taste receptor membrane without affecting responses to salts, acids, sugars or sweet amino acids.[5] Selective inhibition of bitter taste of various drugs by phospholipids such as phosphatidic acid, phosphatidylinositol, soy lecithin, have been reported. Bitter taste of polymyxin B sulfate and trimethoprim sulfamethoxazole (Co- Trimoxazole) have been masked by BMI 60 obtained by fractionating soy lecithin.

Table No 10:-Liposomes.

Drug	Polymer
Quinine, denatortium &propranolol.	Lipoprotein composed of phosphatidic acid and beta lactoglobulin (LC)

14) Mass Extrusion Method

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

15) Use of salt and its Derivative

In this approach, an attempt is made to modify the chemical composition of the drug substance itself, so as to the taste buds. Aspirin tablets can be rendered tasteless by making magnesium salt of aspirin. D-chlorpheniramine maleate is taste-masked salt of chlorpheniramine. The alkyloxy alkyl Carbonates of Clarithromycin have remarkably viated bitterness and improved bioavailability when administered. Sodium salts such as sodium chloride, sodium acetate, sodium gluconate have been shown to be potent inhibitors of some bitter compound. The mechanism is not known, however, research shows that sodium act at peripheral taste level rather than a cognitive effect.

16) Use of amino acid and protein hydrate

Amino acids and their salts (alanine, taurine, glutamic acid, glycine) in combination with bitter drugs reduces the bitterness of the drug for example, taste of ampicillin improved markedly by preparing its granules with glycine and mixing them with additional quantity of glycine, sweeteners, flavour and finally compressing them into tablets.

17) Miscellaneous taste masking Approaches

- **By Effervescent agent**

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, flavouring components, and filers. 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.

- **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 taste79. The antidepressant drug mirtazapine is formulated as an aqueous suspension using methionine (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 80.

- **Continuous multipurpose melt (CMT) Technology**

The CMT method was developed for the continuous granulation and coating of Pharmacologically active substance .it was concluded that this method could be succefully applied for taste masking of bitter drugs.

Evaluation Technique

Sensory evaluation

Taste is a very objective perception depending on individual the perceived taste may be very to different degrees. If we have well controlled experimental set up, it is possibly too accurately and reproducibly measure taste thresholds.to quantitatively evaluate taste sensation following methods have been reported in literature.

- Panel testing (Human subjective)
- Multichannel taste sensor /electronic tongues / Magic tongues
- Measurement of frog taste nerve response
- Spectrophotometric evaluation /D30 value.

❖ **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 solution ranging in taste from tasteless to very bitter. Numerical values are then assigned to these levels of bitterness like 0-5. Subsequently, test solution is tasted and rated on the same scale to assess its bitterness.

Table No 11:-Evaluation test and its methods.

Subjective method	Objective method
Preference Test	Paired Test
Paired Test	Difference Test
Triangle test	Triangle test
Hedonic Scale	Duo trio test, single attribute test
	Ranking test, dilution test

	Analytical, statistical test
	Flavour profile, time intensity test

Frog test nerve responses: In this method, adult bull frog is anaesthetized intraperitoneal 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 responses is then taken as the magnitude of response.

❖ **Electronic Tongue**

This is an automated taste sensing device to detect the magnitude of bitterness of 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 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 substances 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.

❖ **Measurement of frog taste Nerve Response**

In this method, Adult bull frogs are anesthetized intraperitoneal and the glossopharyngeal nerve is then located and dissected from the surrounding tissue and cutproximally.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 formulation taste masked by PA-LG (Phosphatidic acid – lactoglobulin) combination has been reported to be evaluated by this techniques.

❖ **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 100 μg/ml. Generally the taste evaluation involves the objective or analytical method and subjective or hedonic method. Antibiotics are among the most frequently prescribed medications in modern medicine. Antibiotics are used to treat a wide range of infections like respiratory tract infection, urinary tract infection, soft tissue infection, useful in prophylaxis of patients undergoing surgery, in curing gonorrhoea, as well as effective in treatment of typhoid, etc. Most of the antibiotics are bitter in taste and resulting in patient no agreement while administering. Novel drug delivery technologies are revolutionizing drug discovery and development. The challenge in the area of drug delivery is to deliver both existing and emerging drug technologies in a manner that benefits patients.

CONCLUSION

After considering all these factors it is concluded that an ideal taste masking formulation shou ld have following properties:

- Involve least number of equipment's 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.

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