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Review Article

TASTE MASKING TO IMPROVE COMPLIANCE

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Abstract: Taste masking is the main factor in the development of the dosage form. 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. These techniques are not only serves as to mask the taste of drug as well as to enhance the bioavailability of drug dosage form. Commonly used techniques that are adopted for large scale production of pharmaceutical dosage form are use of flavours, coating of drug particle with inert materials, by formation of inclusion complexes, by Molecular complexes of drug with other chemicals**,** Microencapsulation, Multiple Emulsions, Prodrugs **,**using liposome's**,** Dispersion coating and Ion Exchange Resin approach.

Keywords: Taste MaskingTechniques, Factor affecting selection of taste masking techniques, evaluation techniques

INTRODUCTION

It is the defined as the apparent reduction of unpleasant taste by using suitable agent. Taste masking technogies are very important for improving patient compliance and better therapeutics efficacy. Many oral drug delivery formulations have objectionable taste such bitterness, saltiness or sourness[1].

Human detects taste with taste receptor cells that are clustered in to onion-shaped organs called taste buds. Each taste bud has a pore that opens out to surface of the tongue enabling molecules and ions taken into the mouth to reach the receptor cells inside. Human have around 10,000 taste buds which appear in fetus at about three months. A single taste bud contain 50-100 taste cells. Each taste cells receptors on its apical surface. These are transmembrane proteins which bind to the molecules and ions that give rise to the four primary taste sensations namely - salty, sour, sweet and bitter[2].

Taste and its physiology[2,3]

Physiologically, taste is a sensory response resulting from a chemical stimulation of taste buds on the tongue The sense of taste is conducted to the brain by a process called taste transduction. This process begins with the interaction of tastant (i.e., food or medicine) with taste receptor cells in the taste buds. The tastant binds with G-protein coupled receptors in the cells, triggering the release of a G-protein called gustducin.Taste sensation begins when gustducin activates the effector enzymes phosphodiesterase 1A or phospholipase C-2. The effector enzymes then change the intracellular levels of secondary messengers such as cyclic adenosine monophosphate (cAMP), inositol 1, 4, 5-triphosphate (IP3), and diacylglycerol (DAG). The secondary messengers activate ion channels, including calciumchannels inside the cell, and sodium, potassium and calcium channels on the extracellular membrane. This ionization depolarizes the cell, causing the release of neurotransmitters that send a nerve impulse to the brain that carries the signal of taste.

Types of tastes[4]:

These four tastes are located on different receptors on tongue, sensations for sweet are located at tip of the tongue and sensations for sour are located at sides of the tongue whereas bitterness at the back of the tongue and salty sensations are located at the sides and tip of the tongue. Recently, a basic taste umami has been discovered. Umami is the fifth independent taste produced by monosodium glutamate (MSG) contained mainly in seaweed and disodium insinuate (IMP) in meat and fish. These above taste receptors that bind to molecules down by saliva transmit electrical impulses by 7th, 9th and 10th cranial nerves to these areas of brain which participate in perception of taste.

Correlation between the chemical struture of a compound and its taste: [5]

There is a close relationship between chemical structure and taste. Solubility, the degree of ionization, and the type of ions produced in the saliva definitely influence the sensation interpreted by the brain. Sour taste is caused by hydrogen ions, and it is proportional to the hydrogen ion concentration and the lipid solubility of the compound. Saltiness is due to simultaneous presence of anions and cations; eg, potassium bromide, ammonium chloride and sodiumsalicylate. It is characteristics of acids, tannins, alum, phenols, and lactones. High molecular weight salts may have a bitter taste. Sweet taste is due to polyhydroxy compounds, polyhalogenated aliphatic compounds and amino acids. Amino and amide groups, especially if the positive effect is balanced by the proximity of a negative group, may produce a sweet taste.

Sweetness increases with the number of hydroxyl groups, possibly, because of increased solubility. Free bases such as alkaloids and amides gives bitter taste. Polyhydroxy compounds with a molecular weight greater than 300, halogenated substances, and aliphatic thio compounds also may have bitter taste on compounds. Threshold for taste is a minimum concentration of a substance that evokes perception of a taste. The following table gives the threshold concentration of four primary taste sensations. It can be seen that tongue is 10,000 times more senstive to the bitternes of quinine than to sweetness of sugar. Saccharine, on this scale would rate about 0.001%.

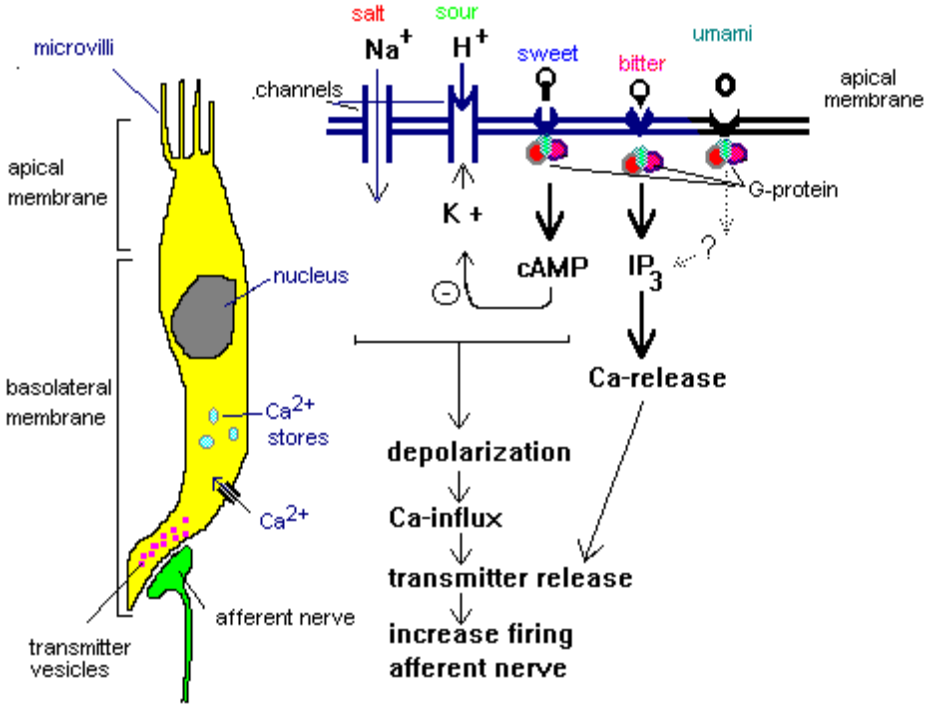


Fig 1. A taste receptor cell

Fig.2 Location Taste on tongue

Table 1: Examples with compounds of pharmaceutical interest, representing each of the four primary tastes [5]

Primary Taste	Functional group(s)	Natural Source	Pharmaceutical Examples	Threshold concentration
Bitter	Organic Amines	Poisons, Alkaloids	Quinine Lopiramide	0.5%
Sour	Organic or inorganic acid	Natural products, Spoiled food	Ascorbic acid Malic acid	0.25%
Sweet	Sugars and sugar analogs	Nutritional and synthetic sweeteners	Fructose Saccharin	0.007%
Salty	Inorganic salts	Sea water, mineral deposits	Sodium chloride NaCl Potassium iodide	0.00005%

Among various approaches two are commonly used to diminish the bitter taste of drug [6]

1. By reducing the solubility of drug in the pH of saliva (5.6 - 6.8).
2. By altering the affinity and nature of drug which will interact with the taste receptor.

Taste masking is not an easy and simple procedure efforts are required before bitter drugs are acceptable for market trials. It needs number of steps. Pharmaceutical industries invest time, money and resources into developing palatable and pleasant tasting products and industries adopt various taste-masking techniques to develop an appropriate formulation. So to avoid unwanted wastage time and money,

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

1) Involve least number of equipments and processing steps.

2) Require minimum number of excipients for an optimum formulation.

3) No adverse effect on drug bioavailability.

4) Require excipients that are economical and easily available.

5) Least manufacturing cost.

6) Can be carried out at room temperature.

7) Require excipients that have high margin of safety.

8) Rapid and easy to prepare

III.Taste masking techniques

To achieve the goal of taste abatement of bitter or unpleasent taste of drug, Various techniques reported in the literature are as follows:

- Addition of flavouring and sweetening agents.
- Microencapsulation
- Coating with inert material
- Ion-exchange.
- Inclusion complexation
- Granulation
- Adsorption
- Prod rug approach
- Taste suppressant and potentiates
- Multiple emulsion technique
- Viscosity enhancer
- pH modifier
- by using liposomes
- By Effervescent agent

A)Taste masking with flavours and sweeteners[7]

This technique is simplest approach for taste masking. Pharmaceutical flavors are classified as natural, artificial, or natural and artificial which are obtained by mixing the natural & synthetic flavors. We have naturally occurring flavouring agents, which can be used in various concentrations such as Anise (3000ppm), Cardamom (550ppm), Wild cherry (50-800ppm), Lemon (1-35ppm), Orange (500ppm), and Peppermint (5000ppm). Natural flavours are comparatively less active than combination of natural and artificial in terms of quality and uniformity. Also these combinations can achieve their aim at very low concentrations. These are generally used in extracts, alcoholic or aqueous solutions, syrups or spirits . These flavors are also used in formulations to mask the bitter taste and give pleasant mouth feel Cooling effect of certain flavouring agent aids in reducing perception of bitterness. The physiology involved is merely to numb taste buds, either rapidly or over a period of time, so that the cooling effects actually build up after ingestion. The brain perceives the coolness even though physically the temperature of the product has not changed.

Some generalization concerning the selection of flavours to mask specific types of taste have been suggested by Janovasky and Wesley. Such recommendations are listed in table 2.and 3

Table 2: Classification of Flavouring Agents

Type	Example	Comment
Natural	Peppermint	Less stable
Artificial	Vanilla	Very stable
Natural and Artificial	Strawberry	Effective at low Concentration

Table 3: Flavour Selection[7][8]

Taste Sensation	Recommended flavour
Salt	Butterscotch, Apple, Apricot, Peach, Vanilla
Bitter	Wild cherry, walnut, Chocolate, mint combination, Passion fruit
Sweet	Fruit and Berry, Vanilla
Sour	Citrus flavour, licorice , Rasp berry

A survey of the taste preferences of human race, as a whole, indicates that sweet taste is very agreeable to our species. Hence for controlling the taste qualities effort are directed to make the preparations sweet to different degrees. Sweeteners are commonly used for this purpose. Table 4 presents a compilation of the most common artificial and natural sweeteners used in pharmaceutical products, their relative sweetness levels, and pertinent comments.

Table 4: Relative sweetness of commonly used sweetner[9]

Sweetening agent	Relative sweetness	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
Manitol	0.60	Nagative heat of solution
Saccharin	450	Unpleasant after taste
Sucrose	1	Most commonly used
Sucralose	600	Synergestic sweetening effect

*Sucrose is taken as standard of 1 for comparison

Active ingredient is significantly objectionable in taste then flavours alone are unable to yield a completely satisfactory product. But this approach can always play a significant Supportive role to other taste masking approach.

Table 5: Sweeteners for Taste Masking[10-12]

Drug	Flavourant / Sweetner	Result
Cetirizine dihydrochloride	Grape, vanilla	Taste masking of the drug achieved.
Cetirizine hydrochloride	Aspartame, sucralose, lemon flavour and citric acid	Optimized taste masked rapid dissolving films was obtained with Aspartame, Sucralose, lemon flavor and citric acid.
Epinephrine	Aspartame, Acesulfame potassium	Combination of ASP and ASK is more effective in reducing bitterness of drug.
Denatonium benzoate	Sodium cyclamate, Zinc sulfate	Mixture of Zinc sulfate and Na cyclamate effective for bitterness inhibition (Zn) and masking (cyclamate).
Ofloxacin	Aspartame	Aspartame significantly masked the taste of tablet

B)Taste masking by microencapsulation[13]

Microencapsulation is a process in which the active moiety (solid or liquid droplets) is coated with a polymeric material or film. Coating the drug particles created a physical barrier between the drug and the taste buds and this taste of active could be masked. Microencapsulation is a valuable technique applicable to protect materials from volatilizing, oxidation as well as to mask their unpleasant taste.

pH independent water insoluble polymers have been used with enteric polymers, inorganic or organic pore formers to achieve taste masking by microencapsulation. Buffering agents are also included in suspending medium to increase taste masking efficiency of microcapsules in oral suspensions. Microencapsulation can be an advantageous taste masking strategy for suspensions due to the low particle size distribution of microcapsules that can remain suspended for a longer time. The technique can be efficiently used for applying higher coating levels

The goal of microencapsulation may be accomplished by any of the following techniques[13]

- Air suspension coating
- Coacervation-phase separation
- Spray drying and spray congealing
- Solvent evaporation
- Multiorifice- centrifugal process
- Pan coating
- Interfacial polymerisation

Table 6 .Taste masking of bitter drugs by microencapsulation[14-20]

Drug	Technique	Polymer	Result
Ibuprofen	air suspension coating	Methacrylic acid copolymer	Chewable taste masked tablet having controlled release characteristics by fluid bed coating, obtained.
Indeloxazine	fluidized bed with side spray method	Hydrogenated oil and surfactant	Taste masking of drug without loss of bioavailability by heat treatment of wax coated microparticles.
Beclamide	simple coacervation	Gelatin, anhydrous sodiumsulfate coacervating agent	Core: wall ratio 1:1, microencapsulation to mask bitter taste.
Clarithromycin	Spray Congealing	Amino Alkyl Methacrylate Polymer E (AMCE)	Taste masking prevented by drug release in the mouth while ensuring rapid release in GIT.
Prednisolone	Solvent Evaporation Technique	Eudragit E 100	Drug polymer 1:10 microspheres of drug are tasteless,further used for formulation into ODT.
Chloroquine diphoshphate	Coacervation Phase Separation	Ethyl cellulose	Taste masking achived

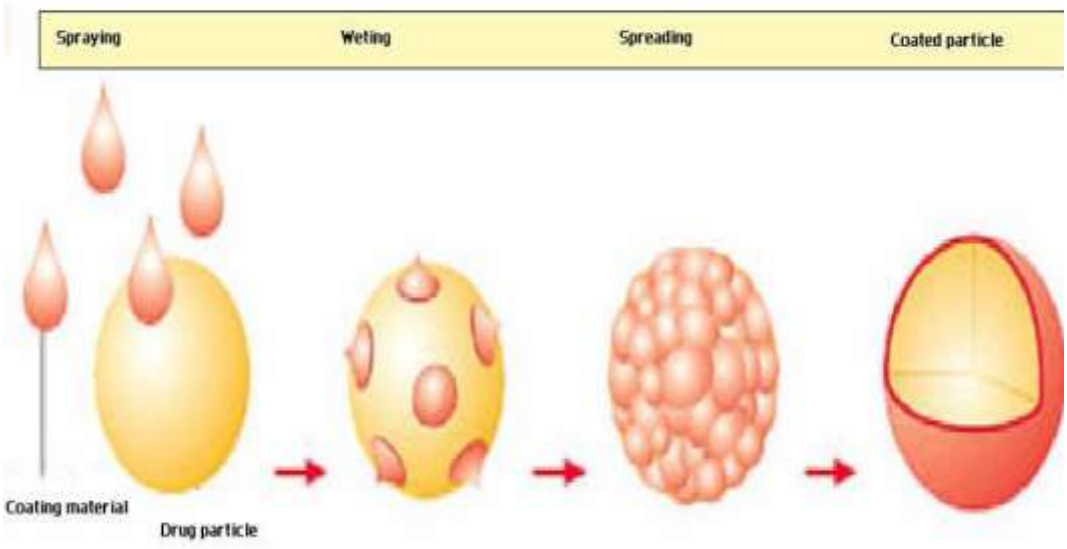


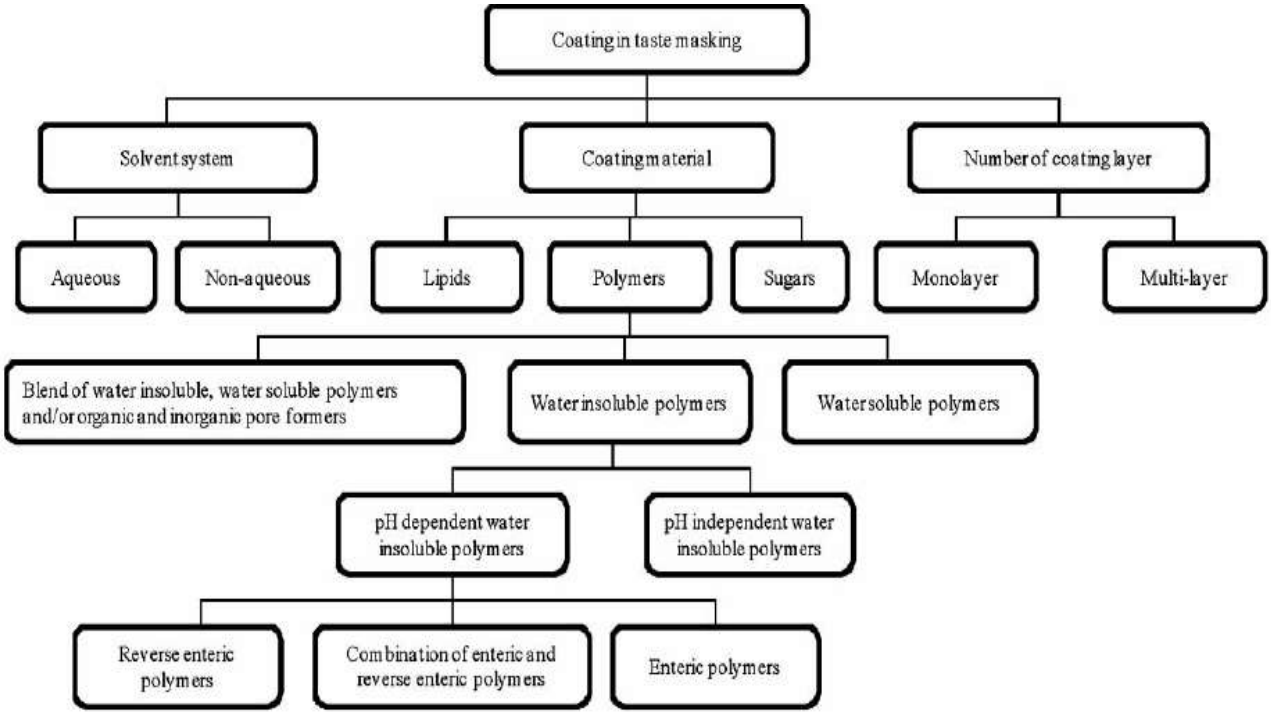
Fig 3. Coating of Drug particle with coating material

C) Coating

Coating is one of the most efficient and commonly used taste masking technologies. In this approach, powders as fine as 50 mm are fluidized in an expansion chamber by means of heat, high-velocity air, and the drug particles are coated with a coating solution introduced usually from the top as a spraythrough a nozzle. Increasing the length of the coating cycle can increase coating thickness the coating. Here, it is classified based on the type of coating material, coating solvent system, and the number of coating layers.[8]

Hydrophobic polymers, lipids, sweeteners and hydrophilic polymers can be used as coating materials, either alone or in combination, as a single or multi-layer coat, to achieve the taste masking by aqueous or organic based coating process.

Multilayer coating has been used to overcome the challenges of coating imperfections, which otherwise lead to decline in the taste masking performance, especially for the aggressively bitter drugs. In which core materials were coated with a first smooth and uniform spacing layer, which can minimize the coating imperfections during the second layer coating and can also act as an instant barrier between the taste receptors and the bitter core material[21].Polymers should be such that it prevents the release of active agent in the oral cavity, following per oral intake, but allows it in stomach or small intestine where the drug is expected to be absorbed. Polymers, which mainly insoluble at salivary pH 6.8 but readily, dissolve at gastric fluid pH 1.2 could be a good candidate for taste masking[22,23]



Classification of patented taste masking strategies based on coating.

Table 7. Taste Masking by Coating[23]

Drug(s)	Coating material(s)	Comments
Acetaminophen	Cellulose acetate(CA) or cellulose acetate butyrate(CAB) and polyvinyl pyrrolidone(PVP)	Coating remains intact on the granules through the compression of the tablet and normal chewing in the mouth with the amount of flavour required being limited to achieve an optimum tablet size
Diphenhydramine Hydrochloride	Blend of water insoluble polymer(e.g. polyvinyl acetate) and(b) a gastrosoluble polymer(e.g. aminoalkyl methacrylate copolymer)	Taste masking was achieved and no tless than about 60% of the drug released in 30minutes
Ciprofloxacin Hydrochloride	Hydratable polymer(e.g. methylcellulose) and water-soluble organic acid and their salts as salivation-promoting agent(e.g. tartaric acid)	Formation of a mouldable viscousmass with a slippery surface in contact with the saliva that considerably facilitates the swallowing of the composition even in high doses
` Cefuroxime Axetil	Reverse enteric polymers(e.g. methyl methacrylate, hydroxy ethyl methacrylate and vinyl pyridine), an enteric polymer (e.g. cellulosic esters like cellulose acetate phthalate) and a pH independent polymer(e.g.cellulosic ethers like EC)	Suitable for medicaments suspended in vehicle having pH 3-5.5, and have a narrow absorption window restricted to upper gastrointestinal tract
Sildenafil citrate	*First coating layer*: water soluble(e.g.hydroxypropylmethyl cellulose) and water insolublepolymers (e.g. EC) *Second coating layer*: saliva-insoluble polymer(e.g. ethylacrylate/methyl methacrylate copolymer) *Third coating layer*: sugar coating(e.g.sucrose)	Taste-masking properties for more than 50 seconds

D)Ion Exchange Resin[24]

Ion exchange resins are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium. An ion exchange resin is an insoluble matrix (or support structure) normally in the form of small (1-2 mm diameter) beads, usually white or yellowish, fabricated from an organic polymer substrate.The material has highly developed structure of pores on the surface of which are sites with easily trapped and released ions. The trapping of ions takes place only with simultaneous releasing of other ions; thus the process is called ion exchange.

Ion exchange resins contain positively or negatively charged functional group and are thus classified as either anionic or cationic exchangers. Within each category, they are classified as strong or weak, depending on their affinity for capable counter ions.

Table 8. Common ion exchange resins[25]

Type	Fuctional Group	Polymer backbone	Commercial resins
Strong Anion	-N+R3	Polystyrene-DVB	Amberlite IR 400, Dowex 1
Weak Anion	-N+R2	Polystyrene-DVB	Amberlite IR 4B, Dowex
Strong Cation	-SO3H	Polystyrene-DVB	Amberlite IR 120, Dowex 50
Weak Cation	-COOH	Methacrylic acid-DVB	Amberlite IRC 50, Indion 204,234, Tulsion 335,339

Typical reactions involved in the gastrointestinal fluids may beenvisaged as follows:

In the stomach:[30] Re-COO-Drug + + HCl → Re-COOH + Drug Hydrochloride

Re-N(CH3)+3 Drug - + HCl → Re-N(CH3) 3 Cl + Acidic drug

In the intestine: Re-COO-Drug + + NaCl → Re-COONa + Drug Hydrochloride

Re-N(CH3)+3 Drug - + NaCl → Re-N(CH3) 3 Cl + Sodium salt of Drug

Table 9. Taste masking by ion exchange resins[26-31]

Drug	Ion exchange resin	Result
Tramadol HCl	Tulsion335	Taste-masked tablet formulated of significant mechanical strength that showed fast disintegration.
Quinine sulphate	Indion 234	The taste masked suspension on release studies showed complete drug release within 20 min.
Levamisole	Amberlite IRP-69	Levamisole Amberlite IRP-69 resinate tablet was stable in mouth and release drug in acidic environment of stomach(93%).
Ondansterone Hydrochloride	Indion 294	Indion 294 provides improved taste masking of Ondansterone Hydrochloride.
Etoricoxib	Indion 204	Taste masking was achieved at drug resin ratio of 1:3.3
Fexofenadine HCl	Indion 234	offers taste masking with good flow properties and drug release.

E) Formation of inclusion complexes[32]

In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent i.e., the host molecule forming a stable complex. The complexing agent is capable of masking the bitter taste of the drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds thereby reducing the perception of bitter taste.

Vander Waals forces are mainly involved in inclusion complexes. Beta-cyclodextrin is most widely used complexing agent for inclusion type complexes. It is sweet, nontoxic, cyclic oligosaccharide obtained from starch. The suppression of bitter taste by cyclodextrin was in increasing order of alpha, gamma, and beta cyclodextrin. Cyclodextrins (CDs) are cyclic oligosaccharides made up of six to twelve D-glucopyranose monomers connected at 1 and 4 carbon atoms. The αCD comprises 6, the βCD 7 and the γCD 8 glucopyranose units.

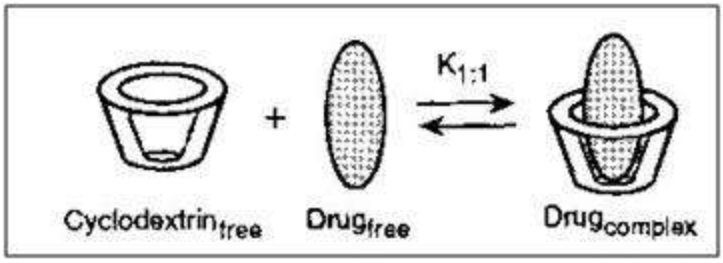


Fig 4. Inclusion complex of Drug with Cyclodextrin

Table 10. Taste Masking By Inclusion complex[33-35]

Drug	Polymer	Result
Primaquine phosphate	Beta – cyclodextrin	Cachets prepared using physical mixture of drug and beta cyclodextrin in ratio of 1:25 showed complete bitter taste masking & easy redispersibilty.
Cetirizine dihydrochloride	alpha - cyclodextrin, Beta – cyclodextrin and gamma-cyclodextrin	B – CD is only recommendable CD for taste masking oral pharmaceutical formulations.
Cefuroxime Axetil	Beta – cyclodextrin	Inclusion complexation with BCD was found to be an excellent method in attaining palatability by masking undesirable taste of Cefuroxime Axetil.
Ibuprofen aqueous Solution	Hydroxypropyl Beta – Cyclodextrin	Taste masking was achieved by weight ratio of Ibuprofen: hydroxypropyl betacyclodextrin 1:11 to1:15.

F)Granulation

Mixture of bitter medicaments and sweeteners, hydrophobic polymers, lipids or waxes can be processed by dry, wet and melt granulation techniques to prepare taste masked oral solid or liquid dosage forms. Granulation is a common procesing step in the production of tablet dosage form. 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. Taste masked pharmaceutical granules, which can be formulated as dry syrup, suspension, conventional chewable or dispersible tablet.

Table 11. Taste Masking by Granulation[36-39]

Drug(s)	Granulating agent(s)	Comments
Tramadol HCL	Ethylcellulose coating, (melt granulation)	Ethylcellulose coating with water soluble excipients (HPMC 6 cps and lactose) proved to be useful as a functional coating to control drug release along with masking bitter taste.
pirenzepine and oxybutynin	EudragitE-100	Taste masked granules, which can be formulated as dry syrup /Suspensions chewable or dispersible tablets.
Diclofenac sodium	Wet granulation	Taste masked diclofenac sodium fast disintegrating tablets using veegum as taste masking agent (1:1.5) and sodium starch glycolate and croscarmellose sodium (5%) as superdisintegrants were successfully prepared.
Norfloxacin	Ethyl Cellulose, HPMC	More acceptabililty than plain film coated tablet. Improved performance and acceptability.

G)Taste masking by adsorption[40]

Adsorbates are commonly used with other taste masking technologies. The drug may be adsorbed or entrapped in the matrix of the porous component, which may result in a delayed release of the bitter active during the transit through the oral cavity thereby achieving taste masking.

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 this dried adsorbates 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.

Table 12.Taste Masking By Adsorption[41]

Drug	Adsorbate	Result
Loperamide	Magnesium aluminium Silicate	further granulating with hydrophobic polymers to achieve taste masking

H) By prodrug approach[42]

A prodrug is chemically modified inert drug precursor which upon biotransformation liberates the pharmaceutically active parent compound. A combination of factors is perhaps operative in the demonstration of a taste response molecular geometry is one of them, for eg, 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.This effect, in turn, may or may not be due to lack of aqueous solubility of the derivative to eliminate the bitter taste response. 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 13. Prodrug for bitter taste masking[43,44]

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

I)Taste Suppressants and Potentiators[45,46]

Lipoproteins are universal bitter taste blockers. Study on animal model showed that lipoproteins composed of phosphatidic acid and lactoglobulin inhibit the taste nerve responses to the bitter substances without affecting those due to the sugars, amino acids, salts or acid Potentiators increase the perception of the taste of sweeteners and mask the unpleasant after taste. Cooling and warming agents suppress unpleasant taste of medicament by subjecting taste receptors to extreme sensations to overpower the bitter taste and confuse the brain. A combination of cooling and warming agents was an effective alternative to achieve taste masking.[19]

Table 14. Taste Suppressants and Potentiators for Taste Masking[21]

Drug(s)	Excipient(s)	Result
Bromhexine	Thaumatin and sugar alcohol(e.g. erythritol and xylitol)	Masks bitter after-taste of Bromhexine
Caffeine	Hydroxyflavanones, their salts andStereoisomers	Suppressants do not have their own taste and work at even very low concentration.
Thymol	Cooling agent(e.g. eucalyptol), warming agent(e.g. methyl salicylate: sweet and fruity compound) and sweet and herbaceous aromatic compounds(e.g. anethole	Mask taste of thymol without using a sugar alcohol.
Paracetamol	*Potentiators:* thaumatine, neohesperidine dihydrochalcone(NHDC), glycyrrhyzin, and their mixtures	Increase the sweetness perception(4 to 5 times) and mask the secondary taste of sweetening agents(metallic or bitter).

J)Multiple Emulsions[47]

A novel technique for taste masking of drugs The w/o/w or o/w/o type multiple emulsions 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'. These phase controls the release of drug from system. Both w/o/w or o/w/o multiple emulsions of chloroquine

phosphate have been prepared and reported to be partially effective in masking the bitter taste of drug.

L) Solid dispersion system[48]

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 glycols of various molecular weights, hydroxy propylmethyl cellulose, urea, manifold and ethyl cellulose Various approaches for preparation 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.

Table 15. Taste Masking by Solid Dispersions[49 50]

Drug	Polymer	Result
Rofecoxib	Poloxamer 188	The melting method was used to prepare solid dispersions and MDT was formulated
Artemether	Mono Amino Glycyrrhyzinate Pentahydrate (GLY)	Results conclusively demonstrated successful masking of taste and rapid disintegration of the formulated tablets in the oral cavity with improved dissolution.

M) Viscosity Enhancers[21]

Suspending coated particles or microcapsules may not be efficient enough to achieve taste masking of highly bitter medicaments in liquid oral suspensions. Usage of viscosity enhancers in these cases would retard the migration of dissolved medicament from the surface of the solid particle to the suspending medium. Additionally, they can also decrease the contact between the bitter medicament and the taste receptors, thus improving the overall taste masking efficiency. Hypromellose was used as a viscosity modifier in taste masked azelastine suspension consisting of sucralose as the sweetening agent. Viscosity enhancers such as xanthan gum,microcrystalline cellulose, and sodium carboxymethylcellulose have been included in suspending vehicle to improve the taste masking efficiency

Table 16.Taste Masking by Viscosity Enhancers

Drug	Viscosity enhancer	Result
azelastine (suspension)	Hypromellose	taste masking achieved

N) pH Modifiers[21]

pH Modifying agents are capable of generating a specific pH microenvironment in aqueous media that can facilitate *in situ* precipitation of the bitter drug substance in saliva thereby reducing the overall taste sensation for liquid dosage forms like suspension.

Table 17.Taste Masking by pH Modifiers

Drug	pH modifier agent	Result
des-quinolone	L-arginine	L-arginine maintains alkaline pH of the suspending vehicle to promote *in situ* precipitation of des-quinolone in saliva.

O) Using liposome's

Entrapment method of masking the obnoxious taste of therapeutic agent is to entrap them into Liposomes. Liposomes are carrier molecules comprising lipids most often in spherical molecules with several layers of lipid, and the drug or biological agent is carried within the lipid molecule. Oils, surfactants, polyalcohols and lipids effectively increase the viscosity in the mouth due to which the decrease in contact between the bitter medicament and the taste receptors, thus improving the overall taste masking efficiency.

Table18.Taste masking of drug by liposomes[50]

Drug	Polymer	Result
Quinine, denatortium and propranolol	Lipoprotein composed of phosphatidic acid(PA) and β-lactoglobulin	PA-LG effectively suppressed the bitter taste of the drugs..
Chloroquine Phosphate	Egg phosphatidyl choline	Chloroquine phosphate was taste masked at pH 7.2 by incorporating into a liposomal formulation.

By Effervescent Agents[51]

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 buckle 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 fillers. Recently, effervescent tablets of fentanyl and prochlorperazine were developed to supply these drugs to the oral cavity for buckle, 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.

Table 19. Taste masking of Drug by Effervescent agent[52]

Drug	Effervescent agent	Result
Fexofenadine Hcl	Sodium bicarbonate, Citric Acid	Fast dissolving tablet fexofenadine HCL indicate that there are no significance change in drug content and in vitro dispersion time.

IV. FACTORS AFFECTING SELECTION OF TASTE MASKING TECHNOLOGY[53]

A. Extent of Bitter Taste

With aggressively bad tasting medicaments even a little exposure is sufficient to perceive the bad taste.

Coating is more efficient technology for aggressively bitter drugs even though coating imperfections, if present, reduce the efficiency of the technique.Similarly, microencapsulation of potent bitter active agents such as azithromycin is insufficient to provide taste masking of liquid oral suspensions.

Viscosity enhancers can complement the taste masking efficiency. Oral suspension containing viscosity enhancers can masquerade the objectionable taste, which arises from the leakage of drug from the coated medicaments or microcapsules.

Conventional taste masking techniques such as the use of sweeteners, amino acids and flavouring agents alone are often inadequate in masking the taste of highly bitter drug

B. 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 flavouring agents to mask the taste of the medicine. For example, low dose palatable paediatric aspirin oral formulation was developed by adding sweeteners, but the same approach failed to address the problem of drugs like acetaminophen because of its high dose. In such cases, coating is preferred to achieve taste masking along with sweeteners to attain an acceptable final dosage form size.

C. Drug Particle Shape and Size Distribution

Particle characteristics of the drug would affect the taste masking process efficiency. Core materials with irregular shapes and small particle size lead to poor taste masking efficiency and varying dissolution of coated particles.

Fines, abrasion and variable coating thickness can lead to situations wherein the taste mask coating is compromised. Multilayer coating using inner spacing layer to sequester the drug from taste masking layer helps to reduce or eliminate such coating imperfections.

D. Dosage Forms

It is estimated that 50% of the population have problem of swallowing tablets, especially the paediatric 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. For formulations which are swallowed unchewed: capsules, coated tablets and slowly disintegrating hard tablets have been used as preferred taste masking technologies. Chewable tablets and liquid oral formulations are preferable in case of large dose drugs for an ease of intake. Taste masking technologies such as sweeteners, particulate coating, microencapsulation and granulation can be employed for chewable tablets and supported with technologies such as viscosity enhancers and pH modifiers to achieve taste masking in liquid oral formulations.

However, this approach suffers from the disadvantage that the polymer coating releases the active agent in an inconsistent fashion and may not provide an immediate release. Moreover, coating is more suitable when the formulation is stored in a dry form. Viscosity enhancers or pH modifiers can be used in the suspending medium to achieve taste masking of suspended coated particles.

E. Drug Solubility

Physicochemical properties of the drug play an important role in the selection of taste masking technology. If drug has a relatively lower water solubility at higher pH, based on which a rapidly disintegrating taste masked composition of drug was formulated by adding an alkalizing agent(sodium bicarbonate) to reduce the water solubility and the consequent taste perception. However, for water soluble drug, the degree of taste masking achieved by simple lipid coating of the drug substance may not be entirely satisfactory, particularly if the product is to be formulated in an aqueous medium. Thus drug was first incorporated into the inner core of a polymeric binder, or a lipid or wax having a melting point higher than that of the outer lipid coating to achieve an efficient taste masking.

F. Ionic Characteristics of the Drug

Ionic characteristics of drugs govern the selection of ion exchange resin polymers and the suitability of the drug candidate for this technology. For example, anionic polymers (e.g. alginic acid) are good candidates for cationic drugs.

V. 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**[54]

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-maske 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 tcehnique.

• **Measurement of Frog Taste Nerve Responses**[55]

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 by PA-LG (phosphatidic acid-lactoglobulin) combination has been reported to be evaluated by this technique.

• **Multichannel Taste Sensor / Magic tongue**[56]

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 characterstics 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 medicnes. 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 though they are being sour rather than bitter. For drugs with both an amino (cationic) groups and a carboxylic acid (anionic) group in the molecule, such as theophylline, caffeine and metronidazole, the electric potential (mV) of channel 1 or 2 did not increase, even though bitterness was observed in human gustatory sensation test. Therefore, different types of membrane component will be needed for a complete evaluation of the bitterness of medicines.

• **Spectrophotometric Method**[57]

A known quantity of the taste-masked formulation is mixed with 10ml 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.

VI. CURRENT & FUTURE DEVELOPMENTS

The word 'medicine' for a child is synonymous with bad taste. Oral pharmaceuticals have been continually adapted for making their *"bitter taste better"*, especially to the paediatric and the geriatric consumers. Taste masking is a viable strategy to improve the patient compliance, especially for bitter drugs, whereby, a gamut of methodologies may be adopted to deliver a palatable formulation. Taste masked products developed from innovative pharmaceutical technologies not only increase the commercial profits, but also create brand value for a company.

Some of the branded products from patented taste masking technologies are Zantac® and Pepcid®. Such intellectual wealth acts as an impetus for emergence of the innovative low cost commercially viable taste masking technologies. Use of sweeteners is an age old and most popular tool for distinguishing bitterness, the present trend has been towards exploring intense sweeteners of natural origin that can hasten commercialization.

Also, the combination of sweeteners with other taste masking technologies including microencapsulation, particulate coating, bitterness blockers, ion exchange resins and potentiators is found to be a more efficient strategy. Improvement in coating technology by use of multiple or spacer layers and a shift to aqueous based coating of hydrophobic polymers are the newer trends. However, the technique requires specialized skills for optimization and scale up of the process.

Granulation, a simpler technology finds more use of swelling polymers for efficient taste masking. Amongst the strategies employed, bitter taste blockers which specifically block the bitter taste but not the pleasant taste of any additive are being explored as universal taste masking alternatives. Presently, they are limited in number, and most of them not being GRAS (Generally Regarded As Safe) listed. With ongoing advancements, using a combination of various taste masking technologies, future looks promising for taste masking of bitter drugs.

CONCLUSION

Taste masking of bitter drugs has been a challenge to the scientist. We have made an attempt to describe various methods, which could be suitable for taste masking of bitter drugs. There are numbers of technologies available, which effectively mask the objectionable taste of drugs but require skillful application, which does not affect the bioavailability of drug. With application of these techniques and proper

evaluation of taste masking effect one can improve product preference to a large extent. Moreover, the development of taste masking methodology requires great technical skill, and the need for massive experimentation.

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