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Review Article

TASTE MASKING TECHNOLOGIES: A REVIEW

SHALINI SHARMA AND SHAILA LEWIS*

Dept of Pharmaceutics , Manipal college of Pharmaceutical Sciences, Manipal University, Manipal 576 104, Karnataka, INDIA

Email : s.lewis@manipal.edu

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ABSTRACT

Oral administration of pharmaceuticals is one of the most popular method of drug dilevery. Many orally administered drugs elicit bitter taste. Palatability is an extremly important factor in ensuring the likelihood that the recepient will intake the pharmaceuticals. A constant problem is in treatment of patient is their inability or unwillingness to swallow solid dosage form such as tablets specially in children and the elderly. These dosage form permit perceptible exposure of active drug ingredient to the taste bud. Accordingly, masking of unpleasent taste characterstics of drug is an important factor in formulation of these agents.*"The worse the taste of the medication, the better the cure"* was once the prevailing attitude. Today a change in patient attitude and development of taste masking technique has reversed this opinion. Patients now expect and demand formulations that are pleasently, or atleast tolerably, flavored.[1] This article reviews the earlier methodologies and approaches of taste masking of bitterness reduction

Key words: Taste masking, Taste bud

INTRODUCTION

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 the tongue enabling molecules and ions taken into the mouth to reach the receptor cells inside.

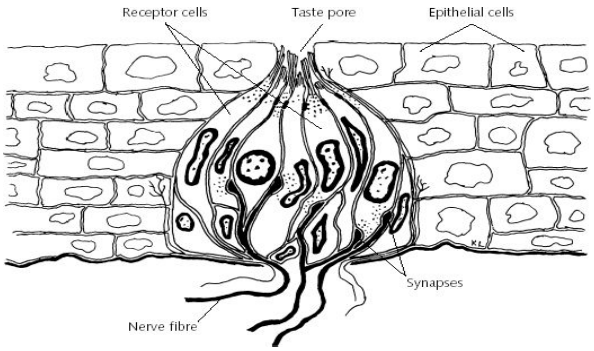

Fig 1 . A taste bud

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.

Recently, a fifth basic taste umami has been discovered. The umami is the taste of certain amino acids (eg., monosodium glutamate).[2,3]

There is often corelation between the chemical struture of a 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 increase[1].

Receptor mechanism involves initial depolarisation at apical receptor site, which causes local action potential in receptor cell. This in turn causes synaptic activation of the primary sensory neuron.

Four basic tastes are confirmed to specific regons of tongue (Table1). But some workers deny the presence of specific regions of the tongue for a particular taste and consider it as a misconception.[2]

Threshold for taste is a minimum concentration of a substance that evokes perception of a taste. The following table 1 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%.

Pharmaceutical companies can save themselves much grief by addressing the taste factor early in the product deelopment. In so doing, they can get their medications to market more quickly, ensure patient compliance, gain market leadersip and reap generous economic rewards. They can also stay in compliance with FDA's final rule, which went into effect December 2000.[5]

So major taste masking efforts are required before bitter drugs are acceptable for market trials. Major taste masking technologies are based on the reduction of solubility of the drug in the saliva so the drug concentration in saliva will remain below taste threshold value. The desire for improved palatibility of formulations has prompted the development of various new technologies for taste abatement. Many of these technologies have been succesfully commercialized. But, the ideal solution of taste masking would be the discovery of universal inhibitor of bitter taste of all drug.

A) Taste masking with flavors and sweeteners

This technique is simplest approach for taste masking . But this approach is not very successful for highly bitter drugs . Artificial sweetners and flavours are generally being used along with other taste-masking techniques to improve the efficiency of these techniques .

Eucalyptus oil is a major constituent of many mouth washes and cough drop formulations which is a bitter tasting substance. Its bitter taste can be masked by agent including fenchone, borneol or isoborneol[6]

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 effect actually build up after ingestion. The brain perceives the coolness even though physically the temperature of the product has not changed.[7]

Some generalization concerning the selection of flavors to mask specific types of taste have been suggested by Janovasky and Wesley.[8] Such recommendations are listed in table 3.

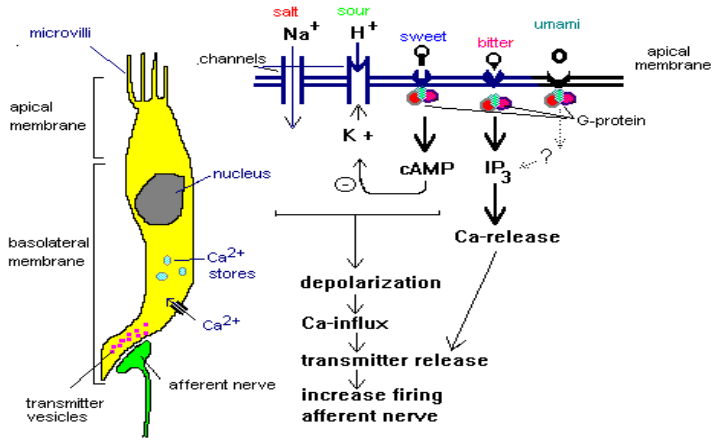

Fig 2 . A taste receptor cell

Table 1: Specific area of tongue and threshold concentration for primary taste sensations[4]

Taste	Area of tongue	Threshold concentration
Sweet(sucrose)	Tip of tongue	0.5%
Salt(Nacl)	Tip and sides of tongue	0.25%
Sour(HCl)	Sides of tongue	0.007%
Bitter(Quinine)	Back of tongue	0.00005%

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
- Ion-exchange.
- Inclusion complexation
- Granulation
- Adsorption
- Prodrug approach
- Bitterness inhibitor
- Multiple emulsion technique
- Gel formation
- Miscellenous

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[8]

Taste sensation	Recommended flavor
Salt	Butterscotch, apple, apricot, peach,vanilla
Bitter	Wild cherry, walnut, chocolate, mint combinations, passion fruit
Sweet	Fruit and berry, vanilla
Sour	Citrus flavors, licorice, root beer, raspberry

A combination of flavoring agents is usually employed. Flavor adjuvants like menthol and chloroform are considered as a desenstizing agents because addition to their own odor and flavor they also have mild anaesthetic effect on taste receptors.

Aspirin medicated floss contains sodium phenolate as an anaesthetizing agent in addition to chocolate flavor to mask the bitter taste of aspirin[9]

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

Table 4: Relative sweeteness of commonly used sweeteners[10]

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

*Sucrose is taken as a standard of 1 for comparison.

Aspartame is used as prominent sweetner in providing bitterness reduction. A very small concentration (0.8%) is effective in reducing bitterness of 25% acetaminophen. Cyclamates have been banned by the USFDA since 1970 due to its carcinogenic effect.

The neohesperidine dihydrochalone is an artificial bitterness suppressor and flavor modifier. It is a open chain analogue of neohesperidine, a bitter flavanone that occurs in seville oranges (citrus aurantium). Taste masking properties of the neohesperidine dihydrochalone have been reviewed by Cano et al. It is a bitterness supressor and flavor modifier that also elicits a very intense lingering sweet taste. Due to its lingering sweet taste the taste of bitter substance appears later in time and taste could be masked.

Table 5: Taste masking of drug by flavors and sweeteners

Drugs	Taste	Taste masking agents	Dosage forms	References
Eucalyptus oil	Bitter	Fenchone, borneol	Mouth washes	6
Ibuprofen	Bitter	Saccharin sodium sucrose, sorbitol solution	Syrup, suspension	12,13
Thymol, Triclosan	Bitter	Citrus flavor, limonene	Oral rinses	11
Zinc acetate dihydrate	Bitter	Saccharin sodium	Lozenges	14

Active ingredient is significantlly objectionable in taste then flavours alone are unable to yield a completely satisfactory product. Major taste masking efforts are required before they are acceptable for market trials. But this approach can always play a significant supportive role to other taste masking approach.

B) Taste masking by microencapsulation

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

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

Advntages

- Taste masking can be achieved with the desirable fast or controlled drug release.
- Bitter liquids may be coated to convert them to solid particles.
- The coated bitter particles can adapt to a wide variety of dosage forms and product applications.
- The goal of microencapsulation may be accomplished by any of the following techniques[8]
- Air suspension coating
- Coacervation-phase seperation
- Spray drying and spray congealing
- Solvent evporation
- Multiorifice- centrifugal process
- Pan coating
- Interfacial polymerisation

In literature first four techniques of microencapsulation have been reported for taste masking purpose, as shown in table 6.

The air suspension coating process can appropriately be described as a upward moving, expanded, fludized bed in central portion of the coating chamber coupled with a downward-moving , more condensed fluidized bed on the periphery of the column.Three types of air suspension coater are available, namely, top spray coater, wurster bottom spray coater and tangential spray coater.[29]

Polymers used for coating

One of the most important factor to be considered in taste masking by coating is selection of coating polymers. Ideally, the coating 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. Choosing one of these polymers is not a simple selection. Before making a decision on coating material following factors must be considered. The particle size of drug, flow characterstics of drug, moisture senstivity, long term stability, temperature of processing and most important, method delivery of active drug molecule.

Cushioning material like Avicel pH 102, microcrystalline cellulose can reduces the rupturing of microcapsule if used as direct compressible diluents.[30]

Table 6: Taste masking of bitter drugs by microencapsulation

Technique	Drug	Coating agent	Dosage form	Reference
Wurster fluid bed coating	Acetaminophen	Croscarmellose	Dispersible tablet	15
	Caffeine/Cimetidine	Eudragit RL 30D, RS30D	Chewable tablet	16
	Ciprofloxacin	Eudragit NE30D/RL30D, HPMC	Oily suspension, sachets	17
	Levofloxacin	Eudragit E100, Cellulose acetate	Suspension	18
Top spray fluid bed coating	Sildenafil citrate	Eudragit NE30D, E-100		19
	Chlorpheniramine maleate	Ethyl cellulose	Mouth melt tablet	20
	Dextromethorphan hydrobromide	PVP-K30		
Tangential spray fluid bed coating	Acetaminophen	Eudragit E-100, Cellulose acetate	Chewable tablet	21
	Theophylline	EudragitNE30D, guar gum	Dry suspension	22
Spray drying	Ampicillin trihydrate	Sodium CMC	Powders	23
	Nizatidine	Eudragit E-100	sprinkels	24
	Roxithromycin	Eudragit RS100 / RL 100	suspension	25
Spray congealing	Clarithromycin	Glyceryl monostearate, Eudragit E100	Powders	26
Coacervation Phase seperation	Chloroquine diphoshphate	Eudragit RS100	Powders	27
Solvent Evaporation	Metronidazole	Eudragit E, Fattibase	Dry Suspension	28

Once the type of coating and the plasticizers (if any) to use have been established then level of coating has to be optimized. If purpose of coating is taste masking, it may be simple taste panel to determine the proper coating level. Thick coating can cause problems both in terms of size and cost apart from being problematic in getting the desired release profile of the drug. However, by coordinating the right type of coating material. It is possibe to completely mask the taste of bitter drug while at the same time, not adversely affecting the intended drug release profile.

Various coating materials for taste masking reported in literature are different grades of Eudragit [31,17,18,19-21,,22,26], cellulose material [15,17,18,20,21, 23,] and waxes [33,26,28] formulations.

C) Taste masking by ion exchange resins

Ion exchange resin are synthetic inert organic polymers consisting of a hydrocarbon network to which ionisable groups are attached and they have the ability to exchange their labile ions for ions present in the solution with which they are in contact.

The most frequently employed polymeric network used is a copolymer of styrene and divinylbenzene (DVB). Apart from this other polymers such as those of acrylic and methacrylic acid crosslinked with divinyl benzene and containing appropriate functional groups, have been used as ion exchange drug carriers.[34,35]

Types of resins

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 7: Common ion exchange resins[34,36,37]

Type	Fuctional group	Polymer backbone	Commercial resins
Strong anion	$-N^+R_3$	Polystyrene-DVB	Amberlite IR 400, Dowex 1
Weak anion	$-N^+R_2$	Polystyrene-DVB	Amberlite IR 4B, Dowex 2
Strong cation	$-SO_3H$	Polystyrene-DVB	Amberlite IR 120, Dowex 50
Weak cation	-COOH	Methacrylic acid-DVB	Amberlite IRC 50, Indion 204,234, Tulsion 335,339

These insoluble ion exchange resins may be supplied in case of cation exchangers as sodium, potassium or ammonium salts and of anion exchangers usually as the chloride. It is frequently necessary to convert a resin completely from one ionic form to another. Charged drugs are normally loaded on to ion exchange resins by two methods, viz, column method and batch method.[34,38]

Column method

In this method a highly concentrated drug solution is passed through a column of resin particles. Since the reaction is an equillibrium phenomenon, maximum potency and efficiency is best obtained by the column method.

Batch method

In this method the drug solution is agitated with a quantity of resin particles until equillibrium is established.

The reaction involved during complexation of drug with resin may be indicated as follows[41]

$Re\text{-}COO^-H^+ + Basic\ drug^+ \rightarrow Re\text{-}COO^-\ Drug^+ + H^+$

$Re\text{-}N(CH_3)^+{}_3Cl^- + Acidic\ drug^- \rightarrow Re\text{-}N(CH_3)^+{}_3\ Drug^- + Cl^-$

Upon ingestion, drugs are most likely eluted from cation exchange resins by H^+, Na^+ or K^+ ions and from anion exchange resins by Cl^-, as these ions are most plentiful available in gastrointestinal secretions.

Typical reactions involved in the gastrointestinal fluids may be envisaged as follows:

In the stomach:

$Re\text{-}COO^-Drug^+ + HCl \rightarrow Re\text{-}COOH + Drug\ Hydrochloride$

$Re\text{-}N(CH_3)^+{}_3\ Drug^- + HCl \rightarrow Re\text{-}N(CH_3)_3\ Cl + Acidic\ drug$

In the intestine:

$Re\text{-}COO^-Drug^+ + NaCl \rightarrow Re\text{-}COONa + Drug\ Hydrochloride$

$Re\text{-}N(CH_3)^+{}_3\ Drug^- + NaCl \rightarrow Re\text{-}N(CH_3)_3\ Cl + Sodium\ salt\ of\ drug$

Excange capacity

The exchange capacity of an ion exchange resin refers to the number of ionic sites per unit weight or volume (meq./gram or meq./mL). Sulfonic acid resin derived from polystyrene matrix have lower exchange capacities, about 4 meq/gm, than carboxylic acid resin derived from acrylic acid polymer, about 10 meq/gm, because of bulkier ionic substituents of sulfonic acid resin and polystyrene matrix.[36]

Weak acid cation exchange resins have a pKa value of about 6, so that at pH 4 or above their exchange capacity tends to increase. Ionisation of weak acid cation exchange resin occurs to an appreciable extent only in alkaline solution, i.e., in their salt form. This is reported that their exchange capacity is very low below pH 7 and moderately constant values at pH above about 9.

The rate of ion exchange is influenced by the permeabilty of the solvent and solute through the pores of the resin, whose number and size are influenced by the amount of crosslinking. The diffuson path length is obviously also related to the size of the resin particles.[34,38]

Applications

Ion exchange resins are used in drug formulation to stabilize the senstive components,[39]sustain release of the drug,[40-44] and taste masking (table 9)

Table 8: Literature report on taste masking by ion exchange resins

Drug	Dosage form	Resin used	Reference
Chloroquine phosphate	-	Indion cation exchange resin	45
Ciprofloxacin	-	Lewatit CNP	46
Dextromethorphan hydrobromide	Dry / liquid suspension	Carbomer 934	47
Ephedrine hydrochloride	-	Indion CRP 244/254	48
Erythromycin, clarithromycin	Liquid suspension	Carbomer 934	49,50
Orbifloxacin	Dry / liquid suspension	Amberlite IRP64/69	51
Paroxetin hydrochloride	Liquid suspension	Amberlite IRP88	52
Ranitidine hydrochloride	Chewable tablet	Amberlite IRP69/88	53
Remacemide hydrochloride	Dry / liquid suspension	Amberlite IRP64	54

Interaction of amine drugs with polycarboxylic acid ion exchange resin [50-55] indicated that these resins may be quite useful in taste coverage. These studies indicated that saliva, with an average pH of 6.7 and a cation concentration of 40meq/l, would only elute a limited percentage of drug from adsorbate. However rapid elution would occur as soon as the adsorbates is exposed to the low pH of the stomach. The particle coating of polycarboxylic acid ion exchange resin adsorbates can also be considered as a method for achieving taste coverage. This is beneficial because the taste coverage ability of the uncoated adsorbate.

D) Taste masking by formulation of inclusion complexes

Inclusion complexs are 'host-guest' relationship in which complexing agent act as host and provide cavities in which foreign

guest molece may fit. Cyclodextrin form inclusion types of complexes with organic molecules both in solid state and in solution.[56]

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

B-cyclodextrin is most widely used complexing agent for inclusion type complexes. It is sweet, non toxic, cyclic oligosaccharide obtained from starch.

Carbepentane citrate can be formulated in palatable liquid formulation with 50% reduced bitterness by forming 1:1 complex with cyclodextrin. Similarly a 1:11 to 1:15 inclusion complex of ibuprofen and hydroxy propyl-β-cyclodextrin can be formulated as palatable solution.[57]

Bitter amine drugs such as chloroquine phosphate can be treated with tannic ad for taste abatement purpose.[58]

Bitter taste of dimenhydrinate can be masked by forming a porous drug-polymer matrix with an copolymer hanving a plurality of carboxylic acid and ester groups, eg., Eudragit S-100[5]

Table 9: Taste masking of bitter drug by complexation

Drug	Complexing Agent	Dosage form	Reference
Benexate hydrochloride	Cyclodextrin	Granules	57
Carbepentane citrate	Cyclodextrin	Oral liquid	57
Chloroquine phosphate	Tannic acid	Syrup	58
Dimenhdrinate	Eudragit S-100	Chewable Tablet	59
Gymnema sylvestra	Chitosan	Oral liquid	57
Ibuprofen	Hydroxy propyl-B-cyclodextrin	Solution	57

E) Taste masking by granulation

Granulation is a common procesing 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 lower the effective surface area of the bitter substance that come 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,eg., rapidly disintegrating tablet and chewable tablet.[60]

Taste masked granules of bitter tasting drug pirenzepine and oxybutynin have been prepared by the extrusion using aminoalkyl methacrylate copolymer. (EudragitE-100)[61]

F) 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 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.

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.[62]

G) Taste masking by prodrug approach

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-substarte 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 11).[63]

Table 10. Prodrug for bitter taste masking [64-66]

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

H) Solid dispersion system

Solid dispersion have been defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting(fusion) solvent or melting solvent method. Carriers used in solid dispersion system include povidone, polyethylene glycols of various molecular weights, hydroxy propyl methyl cellulose, urea, mannitol and ethyl cellulose

Various approaches for prepration of solid dispersion are described below-

i) **Melting method:-** In this method, the drug or drug mixture and a carrier are melted together by heating. The melted mixture is cooled & solidified rapidly in an ice bath with vigorous stirring. The final solid mass is crushed & pulverised.

ii) **Solvent method:-** In this method, the active drug and carrier are dissolved in a common solvent, followed by solvent evaporation and recovery of the solid dispersion.

iii) **Melting solvent method**:- In this method drug in solutions is incorporated into molten mass of polyethlene glycol at a temprature 70˚C without removing the solvent[56]

I) Molecular complexes of drug with other chemicals

The solubility and adsorption of drug can be modified by formation of molecular complexes. Consequently lowering drug solubility through molecular complex formation can decrease the intensity of bitterness of drug, Higuchi and pitman, reported that caffeine forms complexes with organic acids that are less soluble than xanthane and as such can be used to decrease the bitter taste of caffeine[56]

J) Taste masking by bitterness inhibitors

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 inhibits 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, sodium gluconate 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.[67,68]

Bitter substances are commonly hydrophobic in nature hence lipoprotein (PA-LG) composed of phophatidic 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.

Bitter taste of brucine, berberine, chloride, caffeine, denatonium benzoate, glycyl L-leucine, L-phenylalanine, naringin, propranolol hydrochloride, quinine hydrochloride, strychnine nitrate and theophylline [69-71] have been suppressed by lipoprotein.

Selective inhibition of bitter taste of various drugs by phospholipids such as phosphatidic acid, phosphatidylinositol, soy lecithin, have been reported.[72] Bitter taste of polymixin B sulfate and trimethoprim-sulfamethoxazole have been masked by BMI 60 obtained by fractionating soy lecithin.[73]

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'. This phase controls the release of drug from system.

These system could be used for controlled-release delivery of pharmaceuticals. If the system is stable enough for a reasonable shelf life, the formulation could also mask the taste of drug. [74]

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. [75]

K) Taste masking by gelation

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 a 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.[76]

L) Miscelleneous taste masking approaches

- **By effervescent agents**

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have been employed for use as taste masking agents for dosage forms that are not dissolved in water prior to administration. A chewing gum composition of bitter medicament was formulated to supply the medicament to oral cavity for local application or for buccal absorption. It comprise a chewing base, an orally administrable medicament, a taste masking generator of carbon dioxide, and optionally a taste bud desensitizing composition (eg, oral anaesthetic such as benzocaine) and other non active material such as sweeteners, flavoring components, and fillers.[77] 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.[78]

- **Rheological modification**

Increasing the viscosity with rheological modifier such as gums or carbohydrates can lower the diffusion of bitter substances from the saliva to the taste buds. Acetaminophen suspension can be formulated with xanthan gum (0.1-0.2%) and microcrystalline cellulose (0.6-1%) to reduce bitter taste[79]. The antidepressant drug mirtazapine is formulated as an aqueous suspension using methonine (stabilizer) and maltitol (thickening agent). Maltitol is stable in the acidic pH range of 2 to 3 and besides masking the unpleasent taste of the drug, it also inhibit its undesirable local anaesthetic effect [80]

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

The CMT method was developed for the continuous granulation and coating of pharmacologically active substances. It was concluded that this method could be succesfully applied for taste masking of bitter drugs [60]

EVALUATION TECHNIQUES

Sensory evaluation

Taste, to think of, is a very subjective perception. Depending on individuals, the perceived taste may vary to different degrees. If we have well controlled experimental set up, it is possible to accurately and reproducibly measures taste thresholds. To quantitatively evaluate taste sensation, following methods have been reported in literature

- Panel testing (human subjects)
- Measurement of frog taste nerve responses.
- Multichannel taste sensor/ magic tongue
- Spectrophotometric evaluation/ D30's value
- **Panel Testing**

The panel testing is a psychophysical rating of the gustatory stimuli. In this method, a group of about 5-10 human volunteers is trained for taste evaluation by using reference solutions ranging in taste from tasteless to very bitter. Numerical values are then assigned to these levels of bitterness (eg.,0-5). Subsequently, test solution is tasted and rated on the same scale to assess its bitterness.

Literature reports panel testing in invariably all the taste-masked frugs 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.[81]

- **Measurement of Frog Taste Nerve Responses**

In this method, adult bull frogs are anaesthetized intraperitoneally and the glossopharyngeal nerve is then located and dissected from the surrounding tissue and cut proximally. An ac-amplifier and an electronic integrator are used to respectively amplify and integrate the nerve impulses. The peak height of the integrated response is then taken as the magnitude of response.

Quinine sulphate formulations, taste masked by PA-LG(phosphatidic acid-lactoglobulin) combination have been reported to be evaluated by this technique[71]

- **Multichannel Taste Sensor / Magic tongue**

This is an automated taste sensing device to detect the magnitude of bitterness of a drug substance. The device has a transducer which is composed of several kinds of lipid/polymer membranes with different 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.[82]

Recently, the technique has been applied, for the quantitative evaluation of the bitternessof 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 comparitively good correlation between the relative response electric potential (mV) of channels 1 or 2 of the taste sensor, which contain negatively charged membranes, and the bitterness as determined by human gustatory sensations tests. Secondly, for anionic drugs, such as diclofenac sodium or salicylic acid, the positively charged membrane in channel 5 or 6 seemed to the useful even through 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.[83]

- **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 evalute the taste masked granules of sparfloxacin, with threshold concentration being 100µg/ml.[84]

CONCLUSION

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

- Involve least number of equipments and processing steps.
- Require minimum number of excipients for an optimum formulation.
- No adverse affect on drug bioavailability.
- Require excipients that are economical and easily available.
- Least manufacturing cost.
- Can be carried out at room temperature.
- Require excipients that have high margin of safety.
- Rapid and easy to prepare.

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