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Research Article

TASTE MASKING OF DRUGS: AN EXTENDED APPROACH

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A B S T R A C T

Taste is an important factor in the development of dosage form. It also gives a unique identity to a product .Taste is mainly a function of taste buds in the mouth.Taste is an important parameter in case of drugs administering orally and is a critical factor. Humans can distinguish among four components of taste: sourness, saltiness, sweetness, bitterness.Bitter and unpalatable taste is a major problem of certain drugs in formulations. Masking the bitter taste of drugs is a potential tool for the improvement of patient compliance which in turn decides the commercial success of the product. Taste masking is a viable and practical strategy to improve the patient compliance .These techniques not only mask the taste of drug, but also may enhance the bioavailability of dosage form.
Unpleasant taste was the biggest barrier for completing treatment in paediatrics. Two approaches are commonly utilized to overcome the bad taste of the drug.The recent techniques of taste masking are inclusion complexation, use ofion exchange resin, mass extrusion, and solid dispersions, coatinggranulation, spray drying, microencapsulation, liposomes, emulsions and gel formation effervescence. Evaluation of taste concealed formulation is done by panel testing, measurement of frog taste nerve response, multichannel taste sensor and spectrophotometricmethod.

INTRODUCTION

Taste

Taste is one of the most important parameters governing patient compliance. A wide variety of active pharmaceutical agents exhibit the bitter taste either during or immediately after oral administration resulting in poor compliance. Although the poor drug compliance due to bitter tasting oral drugs is true for all patient populations, but is significant for paediatric and geriatric medications [1].

The poor palatability and bitter taste were found to be one of the main reasons for non-compliance resulting in a lot of revenue loss to pharmaceutical companies [2-3].

Taste is an important factor in the development of an oral dosage form. Taste can be categorized into five types viz. sweet, sour, salty, bitter, and umami or savoury. Within hours after birth the infants reject bitter taste and prefer sweet and umami taste. Taste buds regenerate every two weeks[4].

Taste Masking

Tastemasking techniques are applied to mask or overcome the bitter or unpleasanttaste of active pharmaceutical ingredients/drugs to achieve patient acceptability andcompliance.

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Aims

Oral administration of bitter or unpleasant tasting drugs is often thebiggest barrier for patient groups, such as paediatrics and geriatrics[5]. A survey ofAmerican Association of Paediatricians reports unpleasant taste as the biggest barrierin the treatment of paediatric population[6].

Unless the active ingredient is tasteless or does not have any unpleasant taste, tastemasking plays a key role in the success of a final solid oral dosage form. The efficiency of tastemasking is often a key determinant for the success of specialized dosage forms like orally disintegrating tablets and films, and chewable tablets. The mechanisms of tastemasking techniques often rely on two major approaches: the first is to add sweeteners, flavours, and effervescent agents to mask the unpleasant taste, and the second is to avoid the contact of bitter/unpleasant drugs with taste buds.

Several techniques have been reported for masking of bitter or undesirable taste of drugs like addition of flavours, sweetener and amino acids, microencapsulation, complexation with cyclodextrin, complexation with ion exchange resin, salt preparation, group alteration and prodrug approach [7-9]. Spray drying has also emerged as one of the simple and viable approach for taste masking.

Taste Buds

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

Salty taste (edge, upper portion)

The salty taste is one among the four taste receptors of tongue. They are located on the edge and upper front portion of the tongue[9]

Sweet taste (tip)

The sweet taste is one among the four taste receptors in the tongue. They are found on the tip of the tongue [9]

Sour taste (along sides in back)

The sour taste is also one of the four taste receptors of the tongue. They occur at sides of the tongue and are stimulated mainly by acids[9]

Bitter taste (back)

The bitter taste is the last and one of the four taste receptors in the tongue. That is located toward the back of the tongue. It is stimulated by a variety of chemical substances, most of which are organic compounds, although some inorganic compounds such as magnesium and calcium also produce bitter sensations[9]

Ideal properties for taste masking process[10]

Any taste masking process should exhibit following properties

1. It should require minimum number of excipients for an optimum formulation.
2. It should have not any adverse effect on drug bioavailability.
3. It should involve least number of equipment's and processing steps.
4. It should be carried out at room temperature.
5. Require excipients that are economical and easily available.
6. Least manufacturing cost.
7. Rapid and easy to prepare.
8. Require excipients that have high margin of safety.

Taste masking techniques

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

1. Addition of flavouring and sweetening agents
2. Microencapsulation
3. Ion-exchange
4. Inclusion complexation
5. Granulation
6. Adsorption
7. Pro-drug approach
8. Bitterness inhibitor
9. Multiple emulsion technique
10. Gel formation
11. Miscellaneous
12. Hot melt coating

Addition of flavouring& sweetening agents

Masking of bitter taste by use of sweeteners is the simple approach. But this approach is notvery successful for highly bitter drugs. Sweeteners and flavours are generally being used alongwith other taste masking techniques to improve the efficiency of this technique. Coolingeffect of certain flavouring agents aids in reducing perception of bitterness. There are a widerange of alternative sweeteners in the market today.

Table 1 presents a compilation of themost common artificial and natural sweeteners used in pharmaceutical products and theirrelative sweetness levels. Synthetic sweeteners such as aspartame and sucralose arecommonly used in most taste masked products. Recently, sweeteners of plant origin such asStevia and glycyrrhizin have emerged as a viable alternative to the artificial sweeteners.

Table 1 List of commonly used sweeteners and their relative sweetness

Sweetening agent	Relative sweetness	Comments	Solubility
Aspartame	200	Less stable in solution	Slightly soluble in ethanol
Glycyrrhizin	50	Moderately expensive	Soluble in water and alcohol
Mannitol	0.60	Negative heat of solution	Soluble in alkali
Saccharin	450	Unpleasant after taste	Rapidly soluble in dilute ammonium solution
Sucrose	1(standard)	Most commonly used	Soluble in water
Stevia	300	Artificial sweetener	

Table 2 Classification of flavouring agents[11]

Type	Example	Comments
Natural	Peppermint	Less stable
Artificial	Vanilla	Highly stable
Natural and artificial	Strawberry	Effective at low concentration

Taste masking by microencapsulation

Microencapsulation is a process by which very tiny droplets or particles of liquid or solidmaterial are surrounded or coated with a film or polymeric material to mask the taste of bitterdrugs as well as to achieve better bioavailability. Coating agents employed in microencapsulation are gelatin, povidone, HPMC, ethyl cellulose, carnauba wax, acrylates and shellac. In this method, bitter drugs are first encapsulated to give free flowing microcapsules which are then blended with excipients and compressed into tablets. Coatingthe active drug with a properly selected polymer film can reduce its solubility and taste couldbe masked.

Types of microencapsulation include

- Air suspension coating
- Coacervation phase separation
- Spray drying
- Spray congealing
- Solvent evaporation
- Pan Coating
- Interfacial polymerization

Taste masking using ion exchange resin

Ion exchange resins are synthetic inert organic polymers consisting of a hydrocarbon networkto which ionisable groups are attached. They have ability to exchange their labile ions forions present in the solution with which they are in contact.

Table 3 Examples of Taste concealed bitter drugs by microencapsulation

Sr.no	Drug	Technique	Coating agent	Dosage form	Ref.
1.	Acetaminophen Caffeine/cimetidine Ciprofloxacin Levofloxacin	Wurster fluid bed coating	Croscarmellose Eudragit RL 30D,RS3OD Eudragit NE30D/RL30D, HPMC Eudragit E100, cellulose acetate	Dispersible tablet Chewable tablet Oily suspension Sachets Suspension	12

The most frequently employedpolymeric network used is a copolymer of styrene and divinyl benzene (DVB). Apart fromthis other polymers such as those of acrylic and Methacrylic acid cross linked with DVB andcontaining appropriate functional groups, have been used as ion exchange drug carriers. Four major types of ion exchange resins are available which are summarized in **Table 4.**

Table 4 Examples of Common Ion exchange resin

Sr.no.	Type	Exchange species	Polymer backbone	Commercial resins	Ref.
1	Strong cation	-SO3H -SO3Na	Polystyrene DVB Sodium polystyrene	Amberlite IR 120, Dowex 50, Indion244, kayron-T-154 Tulsion T-344, Amberlite IPR 69, Indion 254	13
2	Weak cation	-COOH -COO-K+	Meth acrylic acid DVB	Amberlite IRC50, Indion204, kyron-T-104, Kyron-T-114, Tulsion-T-335 Tulsion T-339, Indion 234, kyron-T-134	
3	Strong anion	N+R3	Polystyrene DVB	Amberlite IR400, Indion 454	14
4	Weak anion	N+R2	Polystyrene DVB	Amberlite IR 48, Dowex 2	15

Mechanism of binding of ion exchange resin with drugs:

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 frequentlynecessary to convert a resin completely from one ionic from to another. Charged drugs arenormally loaded on to ion exchange resins by two methods; column method and batchmethod [16, 17].

Column method

Highly concentrated drug solution is passed through the column containing resins. Maximumefficiency is best obtained by the column method.

Batch method

In this method the drug solution is agitated with a quantity of resin until equilibrium isattained.The reaction involved during complexation of drug with resin may be indication[18].

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

$Re\text{-}N^{+}CH_3)3Cl^{-}$ + Acidic $drug^{-} \longrightarrow Re\text{-}N^{+}(CH_3)_3\ Drug^{-} + Cl^{-}$

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 beenvisaged as follows:

In the stomach

Re-COO-Drug+ +HCl ⟶Re-COOH + Drug Hydrochloride

$Re\text{-}N(CH_3)$+3 Drug- + HCl ⟶$Re\text{-}N(CH_3)_3$ Cl + Acidic drug

In the intestine

Re-COO-Drug + + NaCl⟶Re-COONa + Drug Hydrochloride

$Re\text{-}N(CH_3)$ + 3 Drug- + NaCl ⟶$Re\text{-}N+(CH_3)$ 3 Cl + Sodium salt of drug

Inclusion complexation

Inclusion complexes are 'host-guest' relationship in which complexing agent acts as host andcavity act as guest .The complexing agent is capable of masking bitter taste of drug byeither decreasing its oral solubility on ingestion or decreasing the amount of drug particlesexposed to taste buds, thereby reducing the perception of bitter taste. Vander wall forces aremainly involved in inclusion complexes. B-cyclodextrin is most widely used complexingagent for inclusion complex. It is sweet, non-toxic cyclic oligosaccharide obtained fromstarch. Table 5 enlists examples of various drugs taste masked by inclusion complexation.

Table5 Examples of drugs taste masked by inclusion complexes

Drug	Category	Complexing agent used	Ref.
Chloroquine phosphate	Antimalarial	Tannic acid	19
Ibuprofen	NSAID	Hydroxypropyl β-cyclodextrin	20
Benexate hydrochloride	Antiulcer	β -cyclodextrin	21
Metronidazole benzoate	Anti-bacterial	ϒ-cyclodextrin	

Cyclodextrins (CDs) have mainly been used as complexing agents to increase the aqueoussolubility of poorly water-soluble drugs and to increase their bioavailability and stability.

Granulation

Granulation is a less expensive, rapid operation and an easy taste making technique. It is thecommon processing step in the production of tablet dosage form. Some saliva insolublepolymers are used as binding agent. Granules prepared from these polymers show lesssolubility in saliva and thus taste could be masked. Granulations lower the effective surfacearea of the bitter substance that come in contact with the tongue upon oral intake. Tastemasked granules, prepared from saliva insoluble polymer, can be formulated in various typeof tablet dosage form e.g. chewable tablet, rapidly disintegrating tablet.

Liquids and low melting point waxes such as glycerol palmitate stearate, glyceryl behenate andhydrogenated castor oil are commonly used during the granulation to achieve the tastemasking [22]

Adsorption

Adsorption of bitter tasting drug can be considered as the less saliva soluble versions of thesedrugs. Adsorption involves preparing a solution of the drug and mixing it with an insolublepowder that will adsorb the drug, removing the solvent, is dried and used in the preparation ofthe final dosage

form. Many substrates like veegum, bentonite, silica gel and silicates can beused for the preparation of adsorbate of bitter drugs.

Table 6 Examples of drugs taste masked by granulation technology are enlisted in table

Drug(s)	Granulating Agent(s)	Percentage of excipients	Comments	Ref.
Erythromycin	Alginic acid	Drug : polymer Ratio of 2.5:1 to 50:1	Taste masked granules, which can be formulated as dry syrup suspensions/ chewable of dispersible tablets	22
Dextromethorphan	Cyclodextrin	Drug : polymer Ratio of between 0.9:1 and 1:25	Mixing of drug with Cyclodextrin followed by granulation; without complexation	

Table 7 Examples of drugs and adsorbent used in adsorption technique

Sr. No.	Drug	Adsorbent
1	Ranitidine	Magnesium trisilicate
2	Dextromethorphan hydrobromide	Magnesium trisilicate
3	Trimethoprim	Magnesium aluminium silicate(veegum F)
4	Loperamide	Magnesium aluminium silicate(veegum F)
5	Phenyl propanolamine	Magnesium aluminium silicate(veegum F)

Prodrug approach

A prodrug is a medication that is administered in an inactive or less than fully active form, and then it becomes converted to its active form through a normal metabolic process, such as hydrolysis of an ester form of the drug.

Chemical modification, including prodrug design is an effective method for reducing solubility, and improving taste. A prodrug is chemically modified inert drug precursor which upon biotransformation liberates the pharmaceutically active parent compound. Bitterness of a molecule may be due to the efficiency of the taste receptor substrate adsorption reaction which is related to the molecular geometry of the substrate. If alteration of the parent molecule occurs by derivative formation, the geometry is altered, affecting the adsorption constant. Thus the magnitude of a bitter taste response or taste receptor-substrate adsorption constant may be modified by changing the molecular configuration of the parent molecule. The extremely bitter antibiotics have been the focus of much work in reversible drug Modification.

Table8 Examples of antibiotics taste masked by this technique

Drug	Category	Modification done	Ref.
Chloramphenicol	Broadspectrum antibiotic	Palmitateor phosphate ester	23
Clindamycin	Linosamide antibiotic	Alkyl ester	24
Erythromycin	Macrolide antibiotic	Alkyl ester	25
Lincomycin	Lincosamide antibiotic	Phosphate or alkyl ester	26
Tetracycline	Broad spectrum antibiotic	3,4,5-trimethoxybenzoate salts	27

The prodrug approach can be used to increase or decrease the solubility of a drug dependingon its ultimate use. One disadvantage of making a less soluble prodrug (to mask taste) mayresult in compromised bioavailability.There are numerous examples where solubility needs tobe increased. The prime examples involve drugs whose solubility is so low that a solutiondosage form for intravenous usage is not possible.

Bitterness inhibitor

The development of a specific universal inhibitor for bitter taste has been widely required inthe fields of taste physiology. One difficulty in discovery of universal inhibitor for bitter tasteis that a substance that inhibits bitterness of one compound will not influence the bitterness ofa second because many different classes of compound impart bitterness.

Bitter substances are commonly hydrophobic in nature hence lipoprotein (PA-LG) composed of phophatidic acid and B-lacto globulin can mask the target sites for bitter substances on the taste receptor membrane without affecting responses to salts, acids, sugars or sweet aminoacids.

Bitter taste of brucine, berberine, chloride, caffeine, denatonium benzoate, glycyl L-leucine,

L-phenylalanine, naringin, propranolol hydrochloride, quinine hydrochloride, strychninenitrate and theophylline have been suppressed by lipoprotein[28].

Multiple emulsion technique

This is the novel technique used to mask the taste of bitter drugs. Multiple emulsions can beprepared by dissolving drug in the inner aqueous phase of w/o/w emulsion under condition ofgood shelf stability. So that release of drug through oil phase takes place in gastrointestinalmedia[29].

The w/o/w or o/w/o type multiple emulsions are vesicular systems in which active ingredientscan be entrapped in internal phase. The entrapped substances can be transferred from internalphase to external phase through the 'membrane phase'. This phase controls the release ofdrug from systems. These system could be used for controlled – release delivery of pharmaceuticals. If thesystem is stable enough for a reasonable shelf-life, the formulation could also mask the tasteof drug. Both w/o/w and o/w/o multiple emulsions of Chloroquine phosphate have beenprepared and reported to be partially effective in masking the bitter taste of drug [30].

The major problem as regards stability is the presence of two thermodynamically unstable interfaces. Two different emulsifiers are necessary for their stabilization, one with alow HLB for the w/o interface and a second one with a high HLB for the o/w interface. There are several approaches to overcome instability- and release-problems in double emulsions.

Gel formation

Water insoluble gelations on the surface of tablet containing bitter drug can be used fortaste masking. Sodium alginate has the ability to cause water insoluble gelation in presence ofbivalent metal ions. Tablets of amiprolose hydrochloride have been taste masked by applyingan undercoatof sodium alginate and overcoat of calcium gluconate. In presence of saliva,sodiumalginate reacts with bivalent calcium and form water insoluble gel and thus tastemasking achieved [31].

Miscellaneous taste masking approaches

Use of by effervescent agents

Effervescent agents have been shown to be useful and advantageous for oral administrationof drugs and have been employed for use as taste masking agents for dosage forms that arenot dissolved in water prior to administration.

A chewing gum composition ofbitter medicament was formulated to supply the medicament to oral cavity for localapplication or for buccal absorption. It comprise a chewing base, an orally administrable medicament, a taste masking generator of carbon dioxide, and optionally a taste buddesensitizing composition (e.g., oral anaesthetic such as benzocaine) and other non-activematerial such as sweeteners, flavouring components, and fillers [32].

Recently, effervescenttablets of fentanyl and prochlorperazine were developed to supply these drugs to the oral cavity for buccal, sublingual, and gingival absorption. The formulations contain the drug incombination 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 fentanylformulation for further promotion for absorption.

Rheological modification

Increasing the viscosity with rheological modifier such as gums orcarbohydrates can lowerthe diffusion of bitter substances from the saliva to the taste buds. Acetaminophen suspension was formulated with xanthan gum (0.1-0.2%) and microcrystalline cellulose (0.6-1%) toreduce bitter taste.

The antidepressant drug mirtazapine is formulated as an aqueous suspension using ethionine(stabilizer) and maltitol (thickening agent). Maltitol is stable inthe acidic pH range of 2 to 3 and besides, it masks the unpleasant taste of the drug. It alsoinhibitsthe undesirable local anaesthetic effect of the drug.

Continuous multipurpose melt (CMT) Technology

The CMT method was developed for the continuous granulation and coating ofpharmacologically active substances.

Hot melt coating

Polymer coating are widely used to provide drug protection, taste masking, coloration andmodified drug release.

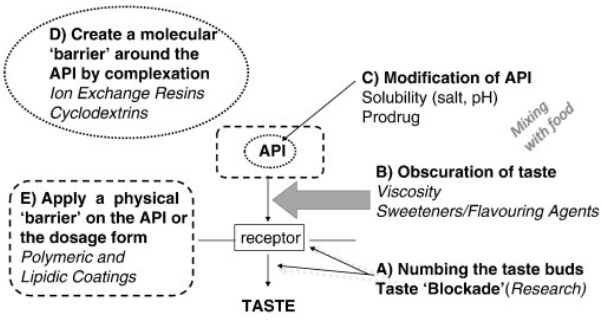

Fig 1 Overview of taste masking methods

Typically, coating polymers must be diluted or dispersed in solvents (water or organic) prior to coating and gliding agents are commonly added to prevent particlesticking throughout processing.

Lipid excipients present an attractive alternative to standardpolymer coatings as they only require melting before application directly onto the substrate.

Solvent evaporation is not required; consequently powders with very high specific surfaceareas can be coated rapidly.

A number of different lipid excipients can be used in coating andchoosing the appropriate excipient for the application requires an understanding of theirphysic-chemical properties and its associated effect on drug release.

Advantages

- Taste masking can be achieved with the desirable fast or controlled drug release
- Bitter liquids may be coated to convert them to solid particles
- The coated bitter particles can adapt to a wide variety of dosage forms and product
- The goal of microencapsulation may be accomplished
- Simple and rapid process
- Control of particle size, shape, porosity and density
- Reproducible and scalable
- Require mild temperature conditions
- Produces free flowing and spherical particles
- Requires no additional processing before compaction into tablet
- Enhanced dissolution rate of drugs
- Cost effective

Evaluation techniques

Tasteis a very subjective perception. Depending on individuals, the perceived taste may vary to different degrees. Still, well controlled experimental set up, can accurately andreproducibly measure taste thresholds. To quantitatively evaluate taste sensation, followingmethods have been reported in literature.

1. Panel testing (human subjects)
2. Measurement of frog taste nerve responses.
3. Multichannel taste sensor/ magic tongue
4. Spectrophotometric evaluation/ D30's value

Panel Testing

This method involves taste comparison between test and reference solutions by group of about 5-10 human volunteers.Reference solutions vary in taste from tasteless to verybitter.Numerical values are then assigned to these levels of bitterness. Subsequently, testsolution is tasted and rated on the same scale to assess itbitterness. This method is easyaccompanied with theaccuracy of human perception of taste against any othergustatoryevaluation technique[33].

Measurement of Frog Taste Nerve Response

In this method, adult bull frogs are anaesthetized intraperitoneally and the glossspharyngealnerve is then located and dissected fromthe surrounding tissue and cut proximally. Anac-amplifier and anelectronic integrator are used to respectively amplify and integratethenerve impulses.

Fig 2 Panel testing apparatus

The peak height of the integrated response isthen taken as the magnitude of response.

Quinine sulphate formulations, tastesmasked byPA-LG (phosphatidiacid-lactoglobulin) combination have been reported to be evaluated by this technique[34].

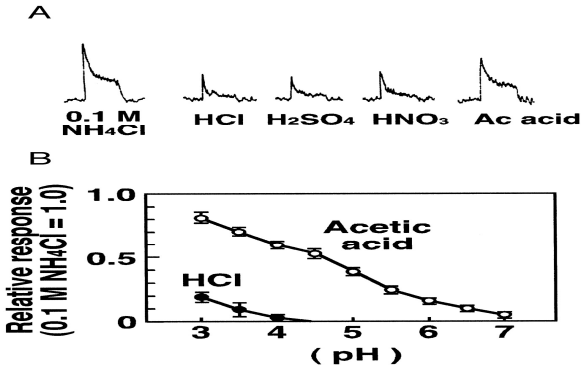

Fig 3 Frog Taste Nerve Response

Multichannel Taste Sensor / Magic tongue

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

The device has a transducer which is composed of several kinds of lipid/polymer membranes the different characteristics that can detect taste in a manner similar to human gustatory sensation. Taste response is transferred into a pattern composed of electric signals of membrane potentials of the receptor part. Different response electric potential pattern are obtained for substance producing different taste qualities [35].

Recently, the technique has been applied, for the quantitative evaluation of the bitterness ofsome commercially available medicines containing quinine, diclofenac sodium, salicylicacid, theophylline, caffeine and metronidazole[36].

Spectrophotometric Method

A known quantity of the taste-masked formulation is mixed with 10ml of distilled water in 10ml syringe by revolving the syringe,end toend, five times in 30 seconds.

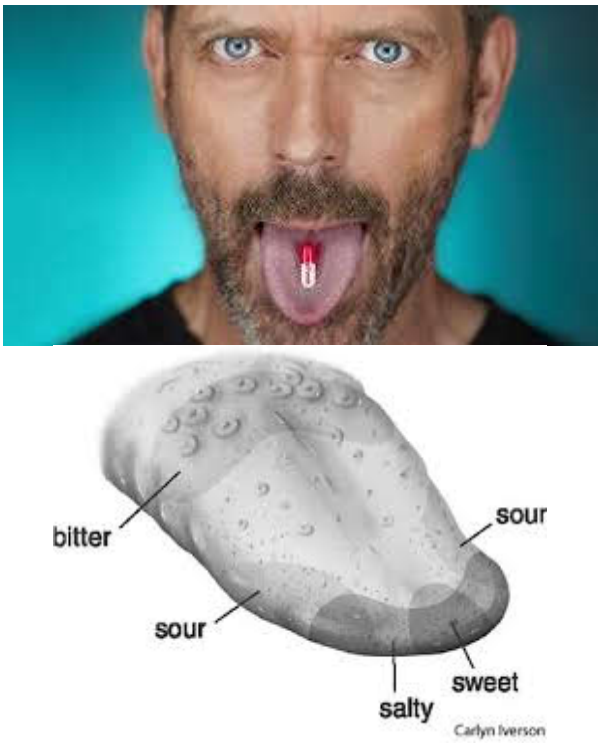

Fig 4 Taste buds of tongue

The test medium isthen filtered through a membrane filter, followed by spectrophotometric determination of theconcentration of the drug in the filtrate.

If this concentration is below the thresholdconcentration, 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, withthreshold concentration being 100µg/ml [37].

CONCLUSION

Taste masking of bitter drug has importance in pharmaceutical industry to gainwidespread marketability. Taste masking techniques is based on thechemical structure of

the drug, physicochemical properties, stability of the drug andexcipients and design of dosage form.

In addition to the taste masking, these techniques mayalso enhance the onset of action as well as bioavailability of drug. Ideal taste masking techniques should not decrease bioavailability and stability of the drug.

New taste masking technologies to mask the bitter taste of drugs are now constantly being developed by the pharmaceutical and drug delivery companies.

After the taste masking some evaluation is also done to evaluate the taste masked drugs. It is used to mask the bitter taste of drug as well as to enhance the solubility, onset of action as well as bioavailability of drug either by any one of above mentioned methods.

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