ABSTRACT
Taste is a critical factor in development of an acceptable oral dosage form. Taste masking is an important factor for bitter drugs to improve the patient compliance especially in the pediatric and geriatric populations. Two approaches commonly used to overcome the bitter taste of drug are reduction of drug solubility in the saliva and alteration of the ability of the drug to interact with taste receptors. These techniques not only mask the taste of drug, but also may enhance the bioavailability of dosage form. The recent techniques of taste masking are inclusion complexation, use of ion exchange resin, mass extrusion, and solid dispersions, coating granulation, spray drying, microencapsulation, liposomes, emulsions and gel formation effervescence. This review emphasizes on the basics of taste, different techniques and patents related to taste masking of drug.

KEYWORDS: Taste Masking Techniques, Physiology of tongue, Taste buds, Ion exchange resins, Prodrug design.

INTRODUCTION
Taste is an important parameter governing patient compliance. Several oral pharmaceutical drug products, food, beverage products and bulking agents, have unpleasant bitter taste due to the components. Masking of the bitter taste of drugs is an important parameter for the improvement of patient compliance. Palatability of oral medications plays an important role
in achieving compliance especially in pediatric products. Any pharmaceutical formulation with a pleasing taste and good flavor would certainly be favored, translate into better compliance and leads to effective therapeutic response. Oral administration of bitter drug requires an acceptable degree of taste masking. In the recent years, enormous development in taste masking technologies has given rise to novel strategies such as child friendly fast dissolving dosage forms, chewable tablets and taste masked suspensions. Ion-exchange reaction, any of a class of chemical reactions between two substances (each consisting of positively and negatively charged species called ions) that involves an exchange of one or more ionic components.

**PHYSIOLOGY OF TASTE**

**TASTE BUDS**

Taste buds are small sense organ in most vertebrates, facilitate in the detection of taste. Hence a group of cells, found especially on the tongue called as taste buds, have been identified on the soft palate, pharynx, epiglottis, which allows different types of taste to be recognized (As shown in figure 1).

![Figure 1: A Taste Bud](image)

Different taste buds like sweet, salt, sour and bitter on tongue are labelled in different colours as shown in figure 2.
Figure 2: Location of taste buds on tongue (5).

Sweet taste (green colour): They are found on the tip of the tongue.

Salty taste (yellow colour): 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.

Sour taste (blue colour): They occur at sides of the tongue and are stimulated mainly by acids.

Bitter taste (purple colour): 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.

Working of taste buds
Taste buds transmit information for different type of taste to brain via nerve fibers. Taste buds for all four types of taste i.e. sweet, sour, salty and bitter shows distinct distribution patterns on the surface of human tongue. Taste buds have been identified on the soft palate, pharynx, and epiglottis. The tongue, soft palate and epiglottis consist of taste buds, which allow human to recognize different tastes in food consumed. The taste buds are chemo receptors; they transmit chemical signals in food into electrical signals. These signals travel to the brain via nervous system for sensation of taste. Taste buds in fishes are distributed over the entire surface of the body to provide information about surroundings.
Effect of age on taste buds

Cells that make up the taste buds with age wear out, as a result taste buds begin to disappear from roof and the sides of the mouth except taste buds that’s are located over tongue. Remaining taste buds becomes less sensitive. Smoking and eating of steaming food may damage to taste buds. This lacking of taste may lead to loss of appetite resulting in poor nutrition. For infants and young children taste is a medium to experience the world of tastes. It is observed that children are more sensitive to certain taste than any adults.

Causes of infected taste buds

Taste buds infection usually occurs due to vitamin B complex deficiency, long-term antibiotics drug therapy following radiation, smoking, vigorous rubbing by a rough tooth and thickening of tissues in elderly and fungal infection (oral thrush) in those with decreased immunity.[6]

TECHNIQUES FOR THE TASTE MASKING OF BITTER DRUGS

1. Taste masking by formulation of inclusion complexes: - Inclusion complexation is a process in which the guest molecule is included in the cavity of host. Guest drug is masked by two approaches firstly by its oral solubility and secondly by decreasing the amount of drug particles exposed to taste buds. β-Cyclodextrins are widely used in industry due to their ability to form inclusion complexes with a variety of molecules. Cyclodextrins are oligosaccharides containing 6, 7, or 8 glucose units. It is sweet and non-toxic oligosaccharides obtained from starch. More than 99% of drugs are complexed with cyclodextrin with 1:1 to mask the bitter taste.

2. Taste masking by granulation: Granulation is a common processing step in the formulation of a dosage form. This step can be used efficiently to mask the taste of a bitter drug. Granules prepared from saliva insoluble polymers as binding agent show less solubility in saliva and taste could be masked. Granulation lowers the effective surface area of the bitter substance that come in contact with the tongue upon oral intake of chewable or tablet dosage forms.[7]

3. Taste masking by means of prodrug technique: Prodrug design is a powerful method for reducing solubility leading to improve taste. A prodrug is chemically changed inert drug precursor which upon biotransformation liberates the pharmaceutically active compound. Bitterness of a molecule can be due to the efficiency of the flavor receptor substrate
adsorption response, that's associated with the molecular geometry of the substrate. If alteration of the discern molecule occurs, it affects adsorption.\textsuperscript{[4]}

4. Gel Formation: Water insoluble gelations 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. Tablets of amiprolese hydrochloride have been taste masked by applying an under coat of sodium alginate and overcoat of calcium gluconate. In presence of saliva, sodium alginate reacts with bivalent calcium and form water insoluble gel and thus taste masking achieved.

5. Multiple emulsion technique: This is the novel technique used to mask the taste of bitter drugs. Multiple emulsions can be prepared by dissolving drug in the inner aqueous phase of w/o/w emulsion under condition of good shelf stability, thus release of drug through oil phase takes place in gastrointestinal media. 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 systems.

These systems 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. Both w/o/w and o/w/o multiple emulsions of chloroquine phosphate have been prepared and reported to be partially effective in masking the bitter taste of drug. There are several approaches to overcome instability and release problems in double emulsions. Two different emulsifiers are necessary for their stabilization, one with a low HLB for the w/o interface and a second one with a high HLB for the o/w interface.

6. Taste masking using ion exchange resin: Ion exchange resins are synthetic inert organic polymers consisting of a hydrocarbon network to which ionisable groups are attached. They have 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 divinyl benzene (DVB). Apart from this other polymers such as those of acrylic and methacrylic acid cross linked with DVB and containing appropriate functional groups, have been used as ion exchange drug carriers.
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 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.

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

Batch method
In this method the drug solution is agitated with a quantity of resin until equilibrium is attained.

The reaction involved during complexation of drug with resin may be indicated as follows.
Re\(^{-}\)COO\(^{-}\)H\(^{+}\) + Basic drug\(^{+}\) → Re\(^{-}\)COODrug\(^{+}\) + H\(^{+}\)
Re\(^{-}\)N\(^{+}\)(CH\(_3\))\(_3\)Cl\(^{-}\) + Acidic drug\(^{-}\) → Re\(^{-}\)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\(^{-}\)COO Drug\(^{+}\) + HCl → Re\(^{-}\)COOH + Drug Hydrochloride
Re\(^{-}\)N(CH\(_3\))\(_3\) Drug\(^{-}\) + HCl → Re\(^{-}\)N(CH\(_3\))\(_3\) Cl + Acidic drug

In the intestine
Re\(^{-}\)COO Drug + + NaCl → Re\(^{-}\)COONa + Drug Hydrochloride
Re\(^{-}\)N(CH\(_3\))\(_3\) + 3 Drug\(^{-}\) + NaCl → Re\(^{-}\)N+(CH\(_3\))\(_3\) Cl + Sodium salt of drug

Exchange 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.

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. Ionization 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 about. Ion exchange resins are used in drug formulation to stabilize the sensitive components, for sustain release of the drug, and for taste masking. Interaction of amine drugs with polycarboxylic acid ion exchange resin 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/1, would only elute a limited percentage of drug from adsorbates. However rapid elution would occur as soon as the adsorbate 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.[8]

7. Taste masking by formation of solid dispersion: 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 glycol of various molecular weights, hydroxy propyl methyl cellulose, urea, mannitol and ethyl cellulose. Various approaches for preparation of solid dispersion are described below:

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

**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.

**Melting solvent method:** In this method, drug in solution is incorporated into molten mass of polyethylene glycol at a temperature 70°C without removing the solvent.

8. Taste masking by use of liposomes: Incorporating into a liposomal formulation prepared with egg phosphotydyl choline masked the bitter taste of chloroquine phosphate in HEPES
(N-2-Hydroxyethylpiperazine-N’-2)-ethane sulfonic acid) buffer at pH 7.2. Bitter substances are commonly hydrophobic in nature hence lipoprotein composed of phosphatidic acid and β-lactoglobulin can mask the target sites for bitter substances on the taste receptor membrane without affecting responses to salts, acids, sugars or sweet amino acids. Selective inhibition of bitter taste of various drugs by phospholipids such as phosphatidic acid, phosphatidylinositol, soy lecithin, has been reported. Bitter tastes of polymyxin B sulfate and trimethoprim sulfamethoxazole have been masked by BMI 60 obtained by fractionating soy lecithin.[7]

LITERATURE REVIEW ON TASTE MASKING TECHNIQUES

Shital J. Bidkar, et al.(2018) reviewed various techniques based on different principles in academic and patent literature for masking of bitter taste of drugs like addition of sweeteners, flavouring agents and amino acids, inclusion complexation with cyclodextrin, salt preparation, pro-drug approach, microencapsulation.[9]

Mangesh R. Bhalekar, et al.(2017) developed taste masking technique for cefixime trihydrate and formulate the taste masked product as dry suspension for pediatric use. Indion 204, a crosslinked acrylic acid polymer based ion exchange resin was used to form a tasteless complex with cefixime.[10]

Sunirmal Bhattacharjee, et al.(2016) studied taste masking of bitter drugs become necessity in case of oral administration and selection of technology depends upon the bitterness of drugs and their compatibility with taste masking agents that does not affect the bioavailability of drug. The main objective of this review was to explore various methodologies for masking the taste of obnoxious drugs, applications, evaluation and also the recent trends in taste masking technologies.[11]

Ajay Bilandi, et al. (2015) formulated taste masked suspension of levofloxacin hemihydrtae, a fluoroquinonone antibiotic. It is mostly used as padiatric suspension in infections. Taste masking of bitter drug is done by Ion exchange resins methods in which different types of resins is used for formulation. After evaluation of different drug resin complex, Tulsion-335 was reported as good taste masking agent.[12]

Rana Zainuddin, et al.(2012) comparative study of taste masking of donepezil hydrochloride using different ion exchange resins. In this study Indion-414, Indion-234,
Indion-214 resins is used in which Indion-414 gives better yield and percentage release as compared to others. Taste masking was performed by batch process.[13]

Shaikh Sana, et al.(2012) studied the formulation and evaluation of taste masked oral suspension of dextromethorphan hydrobromide by using different resins i.e, Ionex QM 1011, Ionex WC 23 and kyron T-114. Ionex QM 1011 was successful in taste masking with good drug loading and percentage drug release.[14]

Sheshala et al.(2011) formulated taste masked microspheres of intensely bitter taste of sumatriptan succinate by coating it with Eudragit EPO using spray drying technique. The taste masked microspheres were incorporated with different types and concentrations of superdisintegrants and compressed using direct compression method followed by sublimation technique. All the tablet formulations disintegrated in vitro within 37-41seconds. The optimized formulation containing 5% Kollidon CL-SF released more than 90% of the drug within 15 min and the release was comparable to that of commercial product (Suminat®). In human volunteers, the optimized formulation was found to have a pleasant taste and mouth feel and disintegrated in the oral cavity within 41seconds.[15]

Birhade et al.(2010) studied the potential of cyclodextrin (β-Cyclodextrin) complexation to mask the bitter taste of Rizatriptan benzoate (RZBT). The taste masking ratio 1:10 of kneading mixture was optimized. In-vitro drug release studies for physical mixture and kneaded system were performed in pH 1.2 and 6.8 buffers. The FTIR, DSC and XRD studies indicated inclusion complexation in physical mixture and kneaded system. Both the binary systems showed effective taste masking and at the same time showed no limiting effect on the drug release. Kneading system showed better results.[16]

Yan et al.(2010) prepared and evaluated a non bitter donepezil HCl orally disintegrating tablet. Taste masking microspheres were prepared with different ratios of donepezil HCl with Eudragit EPO using spray drying technique. It was found that microspheres with a drug – polymer ratio of 1:2 could mask the taste by inhibiting the release of drug in simulated salivary fluid. Microspheres loaded tablets containing polyplasdone NF and low substituted L-HPC both at a 10% level showed rapid disintegration, in vitro (15.5 sec) and in vivo (19.8 sec), which were faster than that of marketed tablets (ARICEPT®).[17]
Akbari et al. (2010) made taste masked Itopride hydrochloride using complexation with ion exchange resin (doshion P 542, Tulsion 344, Indion 234, Indion 204, Kyron T 114) and then incorporated into suspension. The prepared suspensions were evaluated for taste, drug content, particle size, viscosity, sedimentation volume, drug release and accelerated stability studies. From the results, Kyron T 114 was found better taste masking agent. The drug release studies showed that complete drug was released within 20 min.[18]

Patel et al. (2010) prepared taste masked topiramate by ion–exchange resin (Kyron T-104, Kyron T-114, Kyron T-134, Doshion P 542). Ion exchange resins to drug ratio, effect of pH, effect of temperature, effect of resin soaking time, effect of stirring time on complex formulation were optimized. Drug-resin complex were evaluated for swelling, particle size analysis and drug release from drug-resin complex. Kyron T-114 with drug resin ratio of 1:3 was reported best taste masking agent. At gastric pH(1.2), 90% of topiramate was released within 10 minutes.[19]

PATENTS ON TASTE MASKING TECHNIQUES

WO 2017221268 A1 Gokaraju et al.(2017) The invention disclosure taste masking formulations for bitter natural compounds, selected from the extracts, fraction and pure phytochemicals produced in combination with a synthetic polymer or a natural polymer. The invention relates to the novel process of producing the taste masking formulations.[20]

WO 2016024928 A1 Odabasi et al.(2016) This inventions is about taste masked pharmaceutical compositions of paracetamol having bitter taste by using metallic salts.[21]

WO 2014152351 A1 Platt, David et al.(2014) The present disclosure relates to the use of polymers to coat bitter-tasting active pharmaceutical ingredients in a manner that masks the bitter taste of these compounds. Taste masked pharmaceutical formulations in which the particles of pharmaceutically active ingredients are coated with polymers or ion exchange resins are disclosed. The formulations provide taste masked pharmaceutical formulations in which the rapid disintegration of tablets is preserved.[22]

WO 2013175511 A1 Kala, Narayana et al.(2013) This invention comprises an unpleasant taste-masked pharmaceutical composition for oral consumption comprising at least one pharmaceutical active compound of unpleasant taste; the said pharmaceutical composition
comprising an agglomerate of the pharmaceutically active compound/s, at least one sweetener and optionally one or more of diluents/bulking agents, excipients and flavors.[23]

ISSN: 0975-766X Munira Momin et al.(2012) Numbers of herbal origin and chemically synthesized active therapeutics have bitter taste. With the advent of novel formulation techniques as well as novel excipients, the bitter and unacceptable taste can be masked successfully. Formulation attributes in terms of taste, texture and appearance can now be modified to impart better formulation aesthetics. Sugar coating, syrups, lipids, amino acids, proteins are very widely used excipients for taste masking Though the number of polymers are available for film coating, sugar coating technique yet remain versatile in herbal industry.[24]

WO 2008157228 A1 Becicka et al.(2008) invention provides a taste-masked pharmaceutical composition suitable for oral administration comprising a granulated mixture of an active pharmaceutical ingredient and a porous microsphere component, wherein the API is incorporated into the pores of the porous microsphere.[25]

EP 1347781 A1 Bellorini L et al.(2008) discloses oral pharmaceutical compositions which are tasted in the mouth during administration. To mask the taste of unpleasant-tasting active ingredients, it had been found that blending with cyclodextrin without the conventional complex formation is effective. Consequently more economical modes of manufacture such as simple granulation and dry blending can be used.[26]

WO 2005117911 A2 Gayed A. et al.(2006) invented aqueous oral formulations containing sertraline, or a pharmaceutically acceptable salt thereof, and a sulfoalkyl ether cyclodextrin. The liquid formulations were pleasant tasting, convenient to use, and chemically and physically stable. The liquid formulations can be administered directly or diluted before administration. Unlike the commercially available ZOLOFT™ formulation, the liquid formulations herein did not precipitate upon dilution with water, fruit juices, sodas or other pharmaceutically acceptable oral liquid carriers. The sulfoalkyl ether cyclodextrin containing formulation provided significant advantages over the marketed non-aqueous formulation and other cyclodextrin-containing formulations of sertraline.[27]

WO 2006040112 A2 Schwarz et al.(2006) studied the present invention relates to a pharmaceutical composition for oral administration suitable for the preparation of a ready-to-
use suspension comprising coated particles comprising an active substance having an unpleasant or bitter taste, such as clarithromycin, and a suspension base comprising an osmotically active substance capable of providing a high osmolality to the admixture of the suspension base with an aqueous suspending medium in the ready-to-use suspension. Said ready-to-use suspension maintains its palatability over a prolonged period of time by those defined osmotic conditions.[28]

US 5633006 A Edward J. Webman et al.(1997) discloses pharmaceutical composition having reduced bitterness consisting of a bitter pharmaceutical agent, a taste-masking component and a pharmaceutically acceptable carrier. The taste-masking component is an alkaline earth oxide, an alkaline earth hydroxide or an alkaline hydroxide and does not interfere with the activity of the pharmaceutical agent.[29]

US 5286489 Shep K Rose et al.(1994) studied relates to drug-polymer matrix compositions comprising an active ingredient having an amine or amido group and a pharmaceutically acceptable co-polymer having a plurality of carboxylic acid and ester groups wherein the matrix dissociates in a media having a pH of less than 4, thereby releasing the active ingredient into the media.[30]

Patents for taste masking using different techniques with percentage of drug and excipients used in formulation are shown as in table no.1.

Table 1: Patents for taste masking using different techniques.

<table>
<thead>
<tr>
<th>Techniques</th>
<th>Drug</th>
<th>Excipients</th>
<th>Percentage of excipient</th>
<th>Patent No.</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweetener</td>
<td>Acetaminophen</td>
<td>Sucralose</td>
<td>50 to 300 mg of sucralose in 100 ml liquid</td>
<td>MXP04001026 (2005)</td>
<td>32</td>
</tr>
<tr>
<td>Solid dispersion</td>
<td>Levofloxacin</td>
<td>Stearic acid/ palmitic acid</td>
<td>Drug : Fatty acids-1:0.3 to 1:4</td>
<td>VK: EP1194124 (2002)</td>
<td>33</td>
</tr>
<tr>
<td>Ion exchange resin</td>
<td>Sildenafil</td>
<td>Alginic acid</td>
<td>1 to 200 parts anionic polymer substance mixed with 1 part w/w of drug</td>
<td>JP2000119198 (2000)</td>
<td>34</td>
</tr>
<tr>
<td>Microencapsulation</td>
<td>Levofloxacin</td>
<td>Water insoluble enteric coating</td>
<td>Drug: polymer- 0.5 to 1.5 w/w</td>
<td>MXP03008057 (2004)</td>
<td>35</td>
</tr>
</tbody>
</table>
REFERENCES


5. Location of Taste Buds on Tongue Image Available at: https://eschooltoday.com/science/the-five-senses/the-sense-of-taste.html.


