MODERN TASTE CONCEALING TECHNIQUES IN PHARMACEUTICALS: A REVIEW

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ABSTRACT
Taste is a critical factor in development of oral dosage form. Taste masking is important 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. Evaluation of taste concealed formulation is done by panel testing, measurement of frog taste nerve response, multichannel taste sensor and spectrophotometric method.

Keywords: Taste, Taste bud and receptors, Taste masking, Methods, and Evaluation.

1. INTRODUCTION
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 savory. Within hours after birth the infants reject bitter taste and prefer sweet and umami taste. Taste buds regenerate every two weeks. As with many of the senses, taste becomes altered as a function of the aging process, which explains why most children find certain flavors to be too ‘strong’ when adults do not(1).
Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients. To overcome this problem several techniques are evolved to mask the bitter taste of drugs. These techniques not only serve to mask the taste of a drug but also enhance the bioavailability of drug dosage forms. Various methods like coating, inclusion complexes, prodrug approach, microencapsulation, granulation, and adsorption, addition of flavors and sweeteners, ion exchange resins are used for masking the taste of obnoxious drugs (1).

There is often correlation between the chemical structure 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. Receptor mechanism involves initial depolarization at apical receptor site, which causes local action potential in receptor cell. This in turn causes synaptic activation of the primary sensory neuron (1).

2. Ideal properties for taste masking process (2)

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.
7. Rapid and easy to prepare.
8. Require excipients that have high margin of safety.

3. Taste masking techniques

To achieve the goal of taste abatement of bitter or unpleasant taste of drug, various techniques are reported. These are as follows:
3.1 Addition of flavoring and sweetening agents
3.2 Microencapsulation
3.3 Ion-exchange
3.4 Inclusion complexation
3.5 Granulation
3.6 Adsorption
3.7 Prodrug approach
3.8 Bitterness inhibitor
3.9 Multiple emulsion technique
3.10 Gel formation
3.11 Miscellaneous
3.12 Hot melt coating

3.1 Taste masking with flavors and sweeteners
Masking of bitter taste by use of sweeteners is the simple approach. But this approach is not very successful for highly bitter drugs. Sweeteners and flavors are generally being used along with other taste masking techniques to improve the efficiency of this technique. Cooling effect of certain flavoring agents aids in reducing perception of bitterness. There are a wide range of alternative sweeteners in the market today. Table 1 presents a compilation of the most common artificial and natural sweeteners used in pharmaceutical products and their relative sweetness levels. Synthetic sweeteners such as aspartame and sucralose are commonly used in most taste masked products. Recently, sweeteners of plant origin such as stevia and glycyrrhizin have emerged as a viable alternative to the artificial sweeteners (3).

Table 1: List of commonly used sweeteners and their relative sweetness

<table>
<thead>
<tr>
<th>Sweetening agent</th>
<th>Relative sweetness</th>
<th>Comments</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspartame</td>
<td>200</td>
<td>Less stable in solution</td>
<td>Slightly soluble in ethanol</td>
</tr>
<tr>
<td>Acesulfame potassium</td>
<td>137-200</td>
<td>Bitter in higher concentration</td>
<td>Slightly soluble in ethanol</td>
</tr>
<tr>
<td>Glycyrrhizin</td>
<td>50</td>
<td>Moderately expensive</td>
<td>Soluble in water and alcohol</td>
</tr>
<tr>
<td>Mannitol</td>
<td>0.60</td>
<td>Negative heat of solution</td>
<td>Soluble in alkali</td>
</tr>
<tr>
<td>Saccharin</td>
<td>450</td>
<td>Unpleasant after taste</td>
<td>Rapidly soluble in dilute ammonium solution</td>
</tr>
<tr>
<td>Sucrose</td>
<td>1 (standard)</td>
<td>Most commonly used</td>
<td>Soluble in water</td>
</tr>
<tr>
<td>Stevia</td>
<td>300</td>
<td>Artificial sweetener</td>
<td>Soluble in water and ethanol</td>
</tr>
<tr>
<td>Sucralose</td>
<td>600</td>
<td>Synergistic sweetening effect</td>
<td>Freely soluble in water, ethanol and methanol</td>
</tr>
</tbody>
</table>
Table 2: Classification of flavoring agents

<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural</td>
<td>Peppermint</td>
<td>Less stable</td>
</tr>
<tr>
<td>Artificial</td>
<td>Vanilla</td>
<td>Highly stable</td>
</tr>
<tr>
<td>Natural and artificial</td>
<td>Strawberry</td>
<td>Effective at low concentration</td>
</tr>
</tbody>
</table>

3.2 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 and thus taste could be masked. Coating the drug particles creates a physical barrier between the drug and the taste buds and the taste of active could be masked.

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

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 applications.
- The goal of microencapsulation may be accomplished by any of the following techniques.

In literature first four techniques of microencapsulation have been reported for taste masking purposes, as shown Table 3.

1. Air suspension coating

The air suspension coating process can appropriately be described as an upward moving, expanded, fluidized 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 coaters are available, namely, top spray coater, wurster bottom spray coater and tangential spray coater.

2. Coacervation- phase separation
Coacervation-phase separation involves following three steps.
A) Formation of three immiscible chemical phases- The first step of coacervation phase separation involves the formation of three immiscible chemical phases: a liquid vehicle phase, a coating material phase and a core material phase. The three phases are formed by dispersing the core material in a solution of coating polymer, the vehicle phase is used as a solvent for polymer. The coating material phase consists of a polymer in aliquid phase, is formed by using one of the of phase separation- coacervation method, that is by changing the temperature of the polymer solution, by adding a solution, or by inducing a polymer- polymer interaction.

B) Core material phase –The process consists of depositing the liquid polymer coating upon the core material. This is accomplished by controlled, physical mixing of the coating material and the core material in the manufacturing vehicle. Deposition of the liquid polymer coating around the core material occurs if the polymer is absorbed at the interface formed between the core material and the liquid vehicle phase, and this adsorption phenomenon is a prerequisite to the effective coating.

C) Coating material phase- The process involves the rigidizing the coating, usually by thermal, cross-linking or desolvation techniques, to form self-sustaining microcapsule.

3. Spray drying and spray congealing
Spray drying and spray congealing processes are similar in that both involve dispersing the core material in a liquefied coating substance and spraying or introducing the core coating mixture into some environmental condition, whereby, relatively rapid solidification (and formation) of the coating is affected. The principal difference between the two methods is the means by which coating solidification is accomplished. Coating solidification in the case of spray drying is effected by rapid evaporation of a solvent in which the coating material is dissolved. Coating solidification in spray congealing methods, however, is accomplished by thermally congealing a molten coating material or by solidifying a dissolved coating by introducing the coating - core material mixture into a non-solvent. Removal of the non-
solvent or solvent from the coated product is then accomplished by sorption, extraction, or evaporation techniques.

4. Solvent evaporation
The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dissolved in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core coating material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated (if necessary) to evaporate the solvent for the polymer. In the case in which the core material is dispersed in the polymer solution, polymer shrinks around the core. In the case in which core material is dissolved in the coating polymer solution, a matrix-type microcapsule is formed. Once all the solvent for the polymer is evaporated, the liquid vehicle temperature is reduced to ambient temperature (if required) with continued agitation. At this stage, the microcapsules can be used in suspension form, coated on to substrates or isolated as powders.

5. Multiorifice-Centrifugal process
Processing variables include the rotational speed of the cylinder, the flow rate of the core and coating materials, the concentration and viscosity of the coating material, and the viscosity and surface tension of the core material. The Multiorifice-centrifugal process is capable of microencapsulating liquids and solids of varied size ranges, with diverse coating materials.

6. Pan coating
The pan coating process, widely used in the pharmaceutical industry, is among the oldest industrial procedures for forming small, coated particles or tablets. The particles are tumbled in a pan or other device while the coating material is applied slowly. The problem of bitter and obnoxious taste of drug in pediatric and geriatric formulations is a challenge to the pharmacist. In order to ensure patient compliance bitterness masking becomes essential. Molecule interacts with taste receptor on the tongue to give bitter, sweet or other taste sensation, when they dissolve in saliva.

7. Interfacial polymerization
The methods involve the reaction of monomeric units located at the interface existing between a core material substance and a continuous phase in which the core material is dispersed. The continuous or core material supporting phase is usually a liquid or gas, and the
polymerization reaction occurs at a liquid-liquid, liquid-gas, solid-liquid, or solid-gas interface (5).

### Table 3: Examples of Taste concealed bitter drugs by microencapsulation

<table>
<thead>
<tr>
<th>Sr.no</th>
<th>Drug</th>
<th>Technique</th>
<th>Coating agent</th>
<th>Dosage form</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetaminophen Caffeine/cimetidine Ciprofloxacin Levofloxacin</td>
<td>Wurster fluid bed coating</td>
<td>Croscarmellose Eudragit RL 30D,RS30D Eudragit NE30D/RL30D, HPMC Eudragit E100, cellulose acetate</td>
<td>Dispersible tablet Chewable tablet Oily suspension sachets Suspension</td>
<td>6 7 8 9</td>
</tr>
<tr>
<td>2</td>
<td>Sildenafil citrate Chlorpheneramine maleate Dextromethorphan Hydro bromide</td>
<td>Top spray fluid bed coating</td>
<td>Eudragit NE30D, E-100 Ethyl cellulose PVP-K30</td>
<td>Mouth melt tablet</td>
<td>10 11</td>
</tr>
<tr>
<td>3</td>
<td>Acetaminophen Theophylline</td>
<td>Tangential spray fluid bed coating</td>
<td>Eudragit E-100, Cellulose acetate Eudragit NE30D, guar gum</td>
<td>Chewable tablet Dry suspension</td>
<td>12 13</td>
</tr>
<tr>
<td>3</td>
<td>Ampicillin trihydrate Nizatidine Roxithromycin</td>
<td>Spray drying</td>
<td>Sodium CMC Eudragit E-100 Eudragit RS100/RL100</td>
<td>Powders Sprinkles suspension</td>
<td>14 15 16</td>
</tr>
<tr>
<td>4</td>
<td>Clarithromycin</td>
<td>Spray congealing</td>
<td>Glycerimonostearate, Eudragit E100</td>
<td>Powders</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>Chloroquine diphosphate</td>
<td>Coacervation phase Separation</td>
<td>Eudragit RS100</td>
<td>Powders</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>Metronidazole</td>
<td>Solvent Evaporation</td>
<td>Eudragit E, Fattibase</td>
<td>Dry suspension</td>
<td>19</td>
</tr>
</tbody>
</table>

### 3.3 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 (20, 21). Four major types of ion exchange resins are available which are summarized in Table 4.
Table 4: Examples of Common Ion exchange resin

<table>
<thead>
<tr>
<th>Sr.no</th>
<th>Type</th>
<th>Exchange species</th>
<th>Polymer backbone</th>
<th>Commercial resins</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Strong cation</td>
<td>-SO₃H -SO₃Na</td>
<td>Polystyrene DVB</td>
<td>Sodium polystyrene</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amberlite IR 120, Dowex 50, Indion 244, kayron-T-154</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tulsion T-344, Amberlite IPR 69, Indion 254</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Strong anion</td>
<td>N⁺R₃</td>
<td>Polystyrene DVB</td>
<td>Amberlite IR400, Indion 454</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>Weak anion</td>
<td>N⁺R₂</td>
<td>Polystyrene DVB</td>
<td>Amberlite IR 48, Dowex 2</td>
<td>25</td>
</tr>
</tbody>
</table>

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 from to another. Charged drugs are normally loaded on to ion exchange resins by two methods viz, column method and batch method (26,27).

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 (28).

\[ \text{Re-COO-H}^+ + \text{Basic drug}^+ \rightarrow \text{Re-COO-Drug}^+ + \text{H}^+ \]
\[ \text{Re-N}^+(\text{CH}_3)_3\text{Cl}^- + \text{Acidic drug}^- \rightarrow \text{Re-N}^+(\text{CH}_3)_3\text{Drug}^- + \text{Cl}^- \]

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**

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

\[ \text{Re-N(CH}_3\text{)}^+3 \text{Drug}^- + \text{HCl} \rightarrow \text{Re-N(CH}_3\text{)}^+_3 \text{Cl} + \text{Acidic drug} \]

**In the intestine**

\[ \text{Re-COO-Drug} + + \text{NaCl} \rightarrow \text{Re-COONa} + \text{Drug Hydrochloride} \]

\[ \text{Re-N(CH}_3\text{)} + 3 \text{Drug}^- + \text{NaCl} \rightarrow \text{Re-N}^+(\text{CH}_3)_3 \text{Cl} + \text{Sodium salt of drug} \]

**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(26).

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 9.

Ion exchange resins are used in drug formulation to stabilize the sensitive components (29), for sustain release of the drug (30-34), 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/l, would only elute a limited percentage of drug from adsorbates. 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 (35-39).
Taste masking of bitter drugs using in strong acid cation exchangers

![Image of polystyrene beads with sulfonic acid groups and sulfuric acid]

Sulphonation

In sulphonation reaction the polystyrene beads contacted at high temperature with concentrated sulphuric acid. The product is a polystyrene sulphonate, which is a strong acid.

The hydrogen and sodium forms of strong acid resins are highly dissociated and exchange the Na\(^+\) and H\(^+\) are exchange over the entire pH range. The exchange capacity of strong acid resins is independent of solution pH. These resins would be used in the hydrogen form for complete deionization they are used in the sodium form for water softening. After exhaustion, the resin is converted back to the hydrogen form with a sodium chloride solution (40).

Examples of drugs masked using ion exchange resins are given in table 5and 6.

<table>
<thead>
<tr>
<th>Examples of drug</th>
<th>Product name</th>
<th>Matrix</th>
<th>Functional group</th>
<th>Standard ionic form</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine Buflomedil</td>
<td>Amberlite IPR69</td>
<td>Styrene DVB</td>
<td>-SO(_3)H</td>
<td>Na(^+)</td>
<td>41</td>
</tr>
<tr>
<td>Propranolol HCl, dextroamphetamine</td>
<td>Tulsion 344</td>
<td>Styrene DVB</td>
<td>-SO(_3)H</td>
<td>Na(^+)</td>
<td>41</td>
</tr>
<tr>
<td>Erythromycin stearate</td>
<td>Kyron-T-154</td>
<td>Styrene DVB</td>
<td>-SO(_3)H</td>
<td>Na(^+)</td>
<td>41</td>
</tr>
</tbody>
</table>

Weak acid cation exchangers

In a weak acid resin, the ionizable group is a carboxylic acid (COOH) as opposed to the sulfonic acid group (SO\(_3\)H) used in strong acid resins. These resins behave similarly to weak organic acid.
For the weak acid resin to react, it must be dissociated. Therefore, the H⁺ ion in the acid must be taken away by an alkali. For instance, the following reaction is immediate and irreversible

\[
\text{R-COOH} + \text{Na}^+\text{OH}^- \rightarrow \text{R-COO}^-\text{Na}^+ + \text{H}^+\text{OH}^-
\]

This is a neutralization reaction in which the product is water (hence the irreversibility).

Weak acid resins exhibit a much higher affinity for hydrogen ions than strong acid resins. The degree of dissociation of a weak acid resin is strongly influenced by the solution pH. Consequently, resin capacity depends in part of solution pH (44).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiramycin, Dimenhydrinate, Paroxetine, beta-lactam antibiotics</td>
<td>Amberlite IPR64 Methacrylic -COO⁻</td>
<td>H⁺</td>
<td>10meq/kg</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amberlite IPR88 Methacrylic -COO⁻</td>
<td>K⁺</td>
<td>-</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norfloxacin, ofloxacin, Roxithromycin</td>
<td>Tulsion 335 Methacrylic -COO⁻</td>
<td>H⁺</td>
<td>10meq/kg</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroquine phosphate, Quinine sulphate, Ciprofloxacin, Paracetamol</td>
<td>Tulsion 339 Methacrylic -COO⁻</td>
<td>K⁺</td>
<td>-</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefuroxime axetil, Cefpodoximeproxetil, Norfloxacin</td>
<td>Kyron-T-104 Methacrylic -COO⁻</td>
<td>H⁺</td>
<td>-</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ItoprideHCl, Ofloxacin, Tramadol HCl</td>
<td>Kayron-T-114 Methacrylic -COO⁻</td>
<td>H⁺</td>
<td>-</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norfloxacin, ofloxacin, Famotidine, roxithromycin</td>
<td>Indion 204 Methacrylic -COO⁻</td>
<td>H⁺</td>
<td>10meq/kg</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dicyclomine HCl, azithromycin</td>
<td>Indion 214 Crosslinked polyacrylic -COO⁻</td>
<td>H⁺</td>
<td>10meq/kg</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indion 234 Crosslinked polyacrylic -COO⁻</td>
<td>K⁺</td>
<td>-</td>
<td>44</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The process has disadvantages that the resin can be fouled by some substances present in the water (such as organic matter or Fe$^{+++}$ ions).

But in general the advantages of the process (long life of resins, cheap maintenance etc.) outweigh the disadvantages. In addition (47).

### 3.4 Inclusion complexation

Inclusion complexes are ‘host-guest’ relationship in which complexing agent acts as host and cavity act as guest (48). 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 perception of bitter taste. Vander wall forces are mainly involved in inclusion complexes. B-cyclodextrin is most widely used complexing agent for inclusion complex. It is sweet, non-toxic cyclic oligosaccharide obtained from starch. Table 7 enlists examples of various drugs taste masked by inclusion complexation.

**Table 7: Examples of drugs taste masked by inclusion complexes**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Complexing agent used</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine phosphate</td>
<td>Antimalarial</td>
<td>Tannic acid</td>
<td>49</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>NSAID</td>
<td>Hydroxypropyl B-cyclodextrin</td>
<td>50</td>
</tr>
<tr>
<td>Benexate hydrochloride</td>
<td>Antiulcer</td>
<td>B-cyclodextrin</td>
<td>51</td>
</tr>
<tr>
<td>Metronidazole benzoate</td>
<td>Anti-bacterial</td>
<td>7-cyclodextrin</td>
<td>52</td>
</tr>
</tbody>
</table>
Cyclodextrins (CDs) have mainly been used as complexing agents to increase the aqueous solubility of poorly water-soluble drugs and to increase their bioavailability and stability. In addition, CDs have been used to reduce or prevent gastrointestinal or ocular irritation, reduce or eliminate unpleasant smells or tastes, prevent drug or drug additive interactions, or even to convert oils and liquid drugs into microcrystalline or amorphous powders.

3.5 Granulation

Granulation is a less expensive, rapid operation and an easy taste making technique. It is the common processing step in the production of tablet dosage form. Some saliva insoluble polymers are used as binding agent. Granules prepared from these polymers show less solubility in saliva and thus taste could be masked. Granulations lower the effective surface area of the bitter substance that come in contact with the tongue upon oral intake. Taste masked granules, prepared from saliva insoluble polymer, can be formulated in various type of tablet dosage form e.g. chewable tablet, rapidly disintegrating tablet etc. (59).

Liquids and low melting point waxes such as glycerol palmito stearate, glycerylbehenate and hydrogenated caster oil are commonly used during the granulation to achieve the taste masking (60, 61).

Table 8: Examples of drugs taste masked by granulation technology are enlisted in table

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Granulating Agent(s)</th>
<th>Percentage of excipients</th>
<th>Comments</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin</td>
<td>Alginic acid</td>
<td>Drug : polymer Ratio of 2.5:1 to 50:1</td>
<td>Taste masked granules, which can be formulated as dry syrup suspensions/ chewable of dispersible tablets</td>
<td>60</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>Cyclodextrin</td>
<td>Drug : polymer Ratio of between 0.9:1 and 1:25</td>
<td>Mixing of drug with Cyclodextrin followed by granulation; without complexation</td>
<td>61</td>
</tr>
</tbody>
</table>
### 3.6 Adsorption

Adsorption 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, is dried and used 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 (67).

**Table 9: Examples of drugs and adsorbent used in adsorption technique** (68)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adsorbent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranitidine</td>
<td>Magnesium trisilicate</td>
</tr>
<tr>
<td>Dextromethorphan hydrobromide</td>
<td>Magnesium trisilicate</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Magnesium aluminium silicate (veegum F)</td>
</tr>
<tr>
<td>Loperamide</td>
<td>Magnesium aluminium silicate (veegum F)</td>
</tr>
<tr>
<td>Phenyl propanolamine</td>
<td>Magnesium aluminium silicate (veegum F)</td>
</tr>
</tbody>
</table>

### 3.7 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(69).

**Table10: Examples of antibiotics taste masked by this technique**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Modification done</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol</td>
<td>Broad spectrum antibiotic</td>
<td>Palmitate or phosphate ester</td>
<td>70</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Linosamide antibiotic</td>
<td>Alkyl ester</td>
<td>71</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Macrolide antibiotic</td>
<td>Alkyl ester</td>
<td>72</td>
</tr>
<tr>
<td>Lincomycin</td>
<td>Lincosamide antibiotic</td>
<td>Phosphate or alkyl ester</td>
<td>73</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Broad spectrum antibiotic</td>
<td>3,4,5-trimethoxy benzoate salts</td>
<td>74</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Treatment of ulcerative colitis and skin disorder</td>
<td>Diacetate ester</td>
<td>75</td>
</tr>
</tbody>
</table>

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

**3.8 Bitterness inhibitor**

The development of a specific universal inhibitor for bitter taste has been widely required in the fields of taste physiology. One difficulty in discovery of universal inhibitor for bitter taste is that a substance that inhibits bitterness of one compound will not influence the bitterness of a 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 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 have been suppressed by lipoprotein(76).
3.9 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. So that release of drug through oil phase takes place in gastrointestinal media (77).

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 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. 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 (78).

The major problem as regards stability is the presence of two thermodynamically unstable interfaces. 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. There are several approaches to overcome instability- and release-problems in double emulsions.

3.10 Gel formation
Water insoluble gelations on the surface of tabletcontaining bitter drug can be used for tastemasking. Sodium alginate has the ability to causewater insoluble gelation in presence of bivalentmetal ions. Tablets of amiprolose hydrochloridehave been taste masked by applying an undercoatof sodium alginate and overcoat ofcalcium gluconate. In presence of saliva, sodiumalginate reacts with bivalent calcium and form water insoluble gel and thus taste masking achieved (79).

3.11 Miscellaneous taste masking approaches
3.11.1 Use of 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 bittermedicament 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 (e.g., oral anesthetic such as benzocaine) and other non-active material such as sweeteners, flavoring components, and fillers (80). Recently, effervescent tablets 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 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 (81).

3.11.2 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 was formulated with xanthan gum (0.1-0.2%) and microcrystalline cellulose (0.6-1%) to reduce bitter taste(82). The antidepressant drug mirtazapine is formulated as an aqueous suspension using methionine (stabilizer) and maltitol (thickening agent). Maltitol is stable in the acidic pH range of 2 to 3 and besides, it masks the unpleasant taste of the drug. It also inhibits the undesirable local anesthetic effect of the drug(83).

3.11.3 Continuous multipurpose melt (CMT) Technology
The CMT method was developed for the continuous granulation and Coating of pharmacologically active substances(84).

3.12 Hot melt coating
Polymer coating are widely used to provide drug protection, taste masking, coloration and modified drug release. Typically, coating polymers must be diluted or dispersed in solvents (water or organic) prior to coating and gliding agents are commonly added to prevent particle sticking throughout processing. Lipid excipients present an attractive alternative to standard polymer coatings as they only require melting before application directly onto the substrate. Solvent evaporation is not required; consequently powders with very high specific surface areas can be coated rapidly. A number of different lipid excipients can be used in coating and choosing the appropriate excipient for the application requires an understanding of their physic-chemical properties and its associated effect on drug release.
4. Evaluation techniques
Taste is a very subjective perception. Depending on individuals, the perceived taste may vary to different degrees. Still, well controlled experimental set up, can accurately and reproducibly measure taste thresholds. To quantitatively evaluate taste sensation, following methods have been reported in literature

4.1 Panel testing (human subjects)
4.2 Measurement of frog taste nerve responses.
4.3 Multichannel taste sensor/magic tongue
4.4 Spectrophotometric evaluation/D30’s value

4.1 Panel Testing
This method involves taste comparison between test and reference solutions by a group of about 5-10 human volunteers. Reference solutions vary in taste from tasteless to very bitter. Numerical values are then assigned to these levels of bitterness. Subsequently, test solution is tasted and rated on the same scale to assess its bitterness. This method is easy accompanied with the accuracy of human perception of taste against any other gustatory evaluation technique (85).

4.2 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, tastes masked by PA-LG (phosphatidic acid-lactoglobulin) combination have been reported to be evaluated by this technique (86).

4.3 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 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 (87).
Recently, the technique has been applied, for the quantitative evaluation of the bitterness of some commercially available medicines containing quinine, diclofenac sodium, salicylic acid, theophylline, caffeine and metronidazole (88).

4.4 Spectrophotometric Method
A known quantity of the taste-masked formulation is mixed with 10 ml of distilled water in 10 ml syringe by revolving the syringe, end to end, five times in 30 seconds. The test medium is then filtered through a membrane filter, followed by spectrophotometric determination of the concentration of the drug in the filtrate. If this concentration is below the threshold concentration, it may be concluded that the bitter taste would be masked in vivo. This technique has been applied to evaluate the taste masked granules of sparflloxacin, with threshold concentration being 100µg/ml (89).

CONCLUSION
Taste masking of bitter drug has paramount importance in pharmaceutical industry to gain widespread marketability. Taste masking procedure should be rationally selected based on the chemical structure of the drug, physicochemical properties, stability of the drug and excipients and design of dosage form. In addition to the taste masking, these techniques may also enhance the onset of action as well as bioavailability of drug. Ideal taste masking procedure should not decrease bioavailability and stability of the drug.

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