Abstract

Taste, smell and texture are the important factors in development of oral dosage forms. Taste is now a factor influencing the patient compliance and product quality. “The worser the taste of the medication, the better the cure” an older attitude which now totally changed. Taste masking of obnoxious drugs has gained the importance as the most of them are administered orally. This reason is an initiative for the development of various taste masking technologies by which the characteristics of the dosage form is improved and good patient compliance is achieved. The main objective of this review is to explore various methodologies for masking the taste of obnoxious drugs, applications, evaluation and also the recent trends in taste masking technologies.

Keywords: Taste masking, Bitter, Patient compliance, Drug product, Dosage form.

Introduction

Taste has always played an important role in the formulation of oral drug delivery system whether liquid or solid oral dosage forms for the favourable acceptance of oral drugs. As most of the drugs are too bitter to take them in their natural salt form for more patient compliance especially for children and elderly persons.

An ideal taste masking process should effectively mask the taste with the minimum use of excipients, should have no adverse effects, and the excipients should be easily available and economical and be cost effective.

Techniques for the taste masking of bitter drugs:

i. Prodrug approach: - In Prodrug technique is mainly used for the drugs which are effective in their biotransformed form and liberate active metabolite but inactive in their native form. By mainly changing the parent configuration or change in the parent chain structure this approach mainly increases or decreases the adsorption of the drug molecules. It mainly increases drug lipophilicity alter membrane permeability.

ii. Flavours and sweeteners: Sweeteners are commonly used in taste masking of drugs. These are commonly used in combination with other taste masking technologies. These can be mixed with bitter drugs so as to improve the taste of the core material. Sweeteners are classified into natural and synthetic, based on the origin .Synthetic sweeteners such as
sucralose, aspartame, saccharin are showing their prominence in taste masking than the natural ones. These sweeteners are used in combination with sugar alcohols like lactitol, maltitol and sorbitol to decrease their after taste perception. Sucralose can be used with acids (citric acid) to increase the taste masking efficiency of the sweetener. Each sweetener will have their own significance in taste masking and different value of sweetness when compared to standard (Sucrose). There is often a correlation between the chemical structure of a compound and its taste. Low molecular weight salts tend to taste salty where higher molecular weight salts tend toward bitterness. Nitrogen containing compounds, such as the alkaloids, tend to be quite bitter. Flavours are also commonly used in taste masking of drugs in solids and liquid dosage forms. Flavours are classified into natural and artificial. Selection of suitable flavouring agent to be added depends on the original sensation of drug substance (table no:8). The cooling effect of some flavours aids in reducing after-taste perception. Eucalyptus oil is a major constituent of many mouth washes and cough syrup formulations. Examples of various classes of drugs of which the taste masking is achieved by the use of sweeteners and flavouring agents

iii. Coating Polymer/Coating drug particle: - Coating drug particle with the polymers, polymers, lipids as well as sugars can be used as coating material. These can be used alone or in combinations as single layer, multiple layer to achieve taste masking. The coating polymer which does not dissolve in Ph 6.8 but soluble in Ph 1.2 is preferred. For the selection of the coating polymer following factors are to be considered firstly the particle size of the drug, flow characteristics of the drug, long term stability data, moisture sensitivity etc.

iv. 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. For bitter taste forming 1:1 complex with Cyclodextrins. More than 99% of drugs are complexed with cyclodextrin.

v. Taste masking by granulation: - Granulation is a usual and very common processing step in the formulation of a dosage form this step can be used efficiently to mask the taste of a bitter drug. Some saliva insoluble polymers can also work as binding agent, granules prepared from these polymers 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 formulated in the forms of chewable or tablet dosage forms.

vi. Taste masking by ion exchange resins : (IER) — One of the popular approaches for taste of bitter drugs is based on ion exchange resins. Ion exchange resins are synthetic organic polymers inert in nature, consist of a hydrocarbon chain to which insoluble groups are attached and they have ability to exchange their labile ions for ions present in solution with which they are in contact. IER are solid high molecular weight polyelectrolytes that can exchange their ions of equal charge with surrounding medium. These groups have affinity for oppositely charged counter ions. IERs contain positively or negatively charged sites and are classified as cation or anion exchanger. Ion exchanger undergoes reaction with the cations and anions of the surrounding solution respectively. The reaction involved during complexation of drug with resin may be:

\[
\begin{align*}
Re\text{-COO-H} + \text{Basic drug} + & \rightarrow Re\text{-COO-Drug} + H^+ \\
Re\text{-N (CH3) +3Cl^-} + \text{Acidic drug} & \rightarrow Re\text{-N (CH3) +3Drug +Cl^-}
\end{align*}
\]

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

In the stomach

\[
\begin{align*}
Re\text{-COO-Drug} + + HCl & \rightarrow Re\text{-COOH} + Drug HCl \\
Re\text{-N(CH3)}+3\text{Drug} + + HCl & \rightarrow Re\text{-N(CH3)}+3\text{Cl} + \text{Acidic Drug}
\end{align*}
\]

In the intestine

\[
\begin{align*}
Re\text{-COO-Drug} + + NaCl & \rightarrow Re\text{-COONa} + Drug HCl \\
Re\text{-N(CH3)}+3\text{Drug} + + NaCl & \rightarrow Re\text{-N(CH3)}+3\text{Cl} + \text{sodium salt of Drug}
\end{align*}
\]

Exchange capacity

The exchange capacity of IERs refers to the number of ionic sites per unit weight or volume (meq/gram or meq/mL). Sulfonic acid resin derived from polystyrene matrix has lower exchange capacities, about 4 meq/gms, than carboxylic acid resins derived from acrylic acid Polymer, about 10 meq/gms, because of bulkier ionic substituent of Sulfonic acid resin and Polystyrene matrix. Weak acid cation exchange resin have pKa value of about 6, so that pH4 or above their exchange capacity tends to increase. Ionization of weak acid cation exchange resin occurs to appreciable extent only in alkaline solution, i.e. in their salt form. This is reported that their exchange capacity is very low below pH 7 and moderately constant values at pH above about 9. The rate of ion exchange is influenced by the permeability of the solvent and solute through the pores of the resin, whose number and size are influenced by the amount of cross linking. The diffusion path length is obviously also related to the size of the resin particles.

Applications:

IERs are used in drug formulation to stabilize the sensitive components, sustain release of the drug, and taste masking. Interaction of amine drugs with polycarboxylic acid IERs 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 40 meq/L would only elute a limited percentage of drug from adsorbate. However rapid elution would occur as soon as the adsorbates are exposed to the low pH of the stomach. The particle coating of polycarboxylic acid IER adsorbates can also be considered as a method for achieving taste coverage.

vii. Taste masking by microencapsulation: - 
Microencapsulation is a process by which very tiny droplets or particles of liquid or solid material are surrounded or coated with a film or polymorphic material. Coating is an extremely useful technique for a number of applications in pharmaceuticals field. 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 created a physical barrier between the drug and taste buds and taste of active could be masked.

Types of microencapsulation include:

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

<table>
<thead>
<tr>
<th>TECHNIQUE</th>
<th>POLYMER</th>
<th>TASTE MASKED DRUGS</th>
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<tbody>
<tr>
<td>Air suspension coating</td>
<td>Methacrylic acid copolymer</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Phase separation Coacervation</td>
<td>Eudragit E-100, Chitosan</td>
<td>Paracetamol</td>
</tr>
<tr>
<td>Fluidized Bed/Spray coating</td>
<td>Hydrogenated Oil and surfactant</td>
<td>Indeloxazine</td>
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<tr>
<td>Solvent Method Evaporation</td>
<td>Eudragit E, PEG, Ethyl Cellulose</td>
<td>Ofloxacin, Pirezepin</td>
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**TABLE 1: Different methods of taste masking and coating of drug molecule**

**Ideal characteristics of a coating polymer**

- Should not allow the release of drug in oral cavity, but should allow the release of the drug at the expected site (intestine or stomach).
- Should be insoluble in salivary PH (6.8) but should be soluble in gastric PH (1.2)
- Choosing one of the polymers is not a simple selection. Before making the decision on coating Material, the following factors of drug are to be considered.

  - Particle size
  - Flow properties
  - Moisture sensitivity

Once the type of coating and polymer is decided, then the level of coating has to be optimized. Thick coating may cause problems both in terms of size and cost. However, by coordinating the right type of coating material it is possible to mask the bitter taste of the drug completely while at the same time not affecting the intended drug release.

viii. Taste masking by Adsorption: Adsorbates are commonly used with other taste masking technologies. The drug may be adsorbed or
entrapped in the matrix of the porous component, which may result in delayed release of the bitter active during the transit through the oral cavity thereby achieving taste masking. Example: Loperamide formulation with magnesium stearate as adsorbate.

This process involves the adsorption of the drug solution using insoluble materials like silica gel, bentonite, veegum etc. The adsorbate (resultant powder) is dried and used for the formulation of final dosage forms.

**ix. Taste masking by multiple emulsion technique:** A novel technique for taste masking of drugs employing multiple emulsions. 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. The w/o/w or o/w/o type multiple emulsion are vesicular systems in which active ingredients can be entrapped in internal phase. The entrapped substances can be transferred from internal phase to external phase through the membrane phase. This phase controls the release of drug from system.

**x. Taste masking by Gelation technique:**
Water insoluble Gelation on the surface of tablet containing bitter drugs can be used for taste masking. Sodium alginate has the ability to cause water insoluble Gelation in presence of bivalent metal ions. Tablet of amiprolose hydrochloride have been taste masked by applying an undercoat 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.

**xi. 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 includes 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:

1. **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.

2. **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.

3. **Melting solvent method:**

   In this method, drug in solution is incorporated into molten mass of polyethylene glycol at a temperature 700C without removing the solvent.

**xii. Taste masking by viscosity modification:**
Enhancement of viscosity in liquid formulations by thickening agents such as
natural gums or carbohydrates can mask the unpleasant taste of drug by formulating a covering layer on the tongue and act as barrier between drug particles and taste buds, thus lowering the diffusion of drug from saliva into the taste buds13. For viscosity enhancement in liquid formulations, polyethylene glycols and carboxy methylcellulose are induced which not only increases the stability of liquid formulation but surprisingly, provides taste masking of unpleasant tasting medicines. For examples, in cough syrups, terbutaline given in doses of 4mg/5ml can be effectively administered by increasing the viscosity of the formulation.

xiii. **Taste masking by use of bitterness inhibitors:** The development of a specific universal inhibitor for bitter taste has been widely required in the fields of taste physiology and pharmaceutical sciences, but no such inhibitors has been available. One difficulty in discovering of universal inhibitor for bitter taste is that substances that inhibit bitterness of one compound will not influence the bitterness of a second because many different classes of compound impart bitterness. Sodium salts such as sodium chloride, sodium acetate and sodium gluconate have been shown to be potent inhibitor.

xiv. **Taste masking by mass extrusion method:** This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

**Taste masking by use of liposomes:** Another way of masking the unpleasant taste of therapeutic agent is to entrap them into liposome. For example, incorporating into a liposomal formulation prepared with egg phosphotyldyl 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 trimethoprimsulfamethoxazole have been masked by BMI 60 obtained by fractionating soy lecithin.

**Taste masking by use of salts or derivatives:** In this approach, an attempt is made to modify the chemical composition of the drug substance itself, so as to the taste buds. Aspirin tablets can be rendered tasteless by making magnesium salt of aspirin. D-chlorpheniramine maleate is taste-masked salt
of chlorpheniramine. The alkyloxy alkyl Carbonates of Clarithromycin have remarkably viated bitterness and improved bioavailability when administered. Sodium salts such as sodium chloride, sodium acetate, sodium gluconate have been shown to be potent inhibitors of some bitter compound. The mechanism is not known, however, research shows that sodium act at peripheral taste level rather than a cognitive effect.

xvii. Miscellaneous methods:

A. 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 chewable gum composition of bitter medicament was formulated to supply the medicament to oral cavity for local application or 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 example oral anesthetics such as benzocaine and other non-active material such as sweeteners, flavouring components and fillers. Recently, effervescent tablets of fentanyl and prochlorperazine were developed to supply these drugs to the oral cavity for buccal, sublingual and gingival absorption. The formulation contains 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.

B. 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. This provides a taste masked liquid preparation for administration of a relatively large amount of unpleasant tasting medicines. The composition of such a formulation comprises a taste-masking liquid base with a high viscosity induced by thickening agent such as polyethylene glycol and sodium carboxy methyl cellulose. Surprisingly, it has been observed that the high viscosity liquid excipient base provides taste masking benefits to such an extent that extra strength compositions can be prepared with high concentration of bitter tasting ingredients. For example, guaifensine, which is normally administered in doses of not more than 100 mg in 5 ml of liquid, may be administered in doses of 200 mg/ 5 ml, without the feel of bitter taste.

C. Continuous multipurpose melt (CMT) technology:

The CMT was developed for the continuous granulation and coating of pharmacologically active substances. It was concluded that this method could be successfully applied for taste masking of, bitter drug.

Evaluation techniques:

Sensory evaluation:

Taste, to think of, is a very subjective perception. Depending on individuals, the perceived taste may vary to different degrees. If we have well controlled experimental set up, it is possible to accurately and reproducibly measures taste thresholds. To quantitatively evaluate taste sensation, following methods have been reported in literature.
Panel testing:
The panel testing is a psychophysical rating of the gustatory stimuli. In this method, a group of about 5-10 human volunteers is trained for taste evaluation. Numerical values are then assigned to these levels of bitterness like 0-5. Subsequently, test solution is tasted and rated on the same scale to assess its bitterness.

Table 2: Evaluation of taste masking

<table>
<thead>
<tr>
<th>Subjective method</th>
<th>Objective method</th>
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<tbody>
<tr>
<td>Preference test</td>
<td>Difference test</td>
</tr>
<tr>
<td>Paired test</td>
<td>Paired difference test</td>
</tr>
<tr>
<td>Triangle test</td>
<td>Triangle difference test</td>
</tr>
</tbody>
</table>

Hedonic scale
- Duo trio test, single attribute test
- Ranking test, dilution test
- Analytical test, statistical test
- Flavor profile, time intensity test

Frog test nerve responses: In this method, adult bull frog is anaesthetized intraperitonally 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 responses is then taken as the magnitude of response.

Electronic tongue:
This is an automated taste sensing device to detect the magnitude of bitterness of 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 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 substances producing different taste qualities. Recently, the technique has been applied, for the quantitative evaluation of the bitterness of some commercially available medicines. Quinine hydrochloride was taken as the standard for bitterness. Basic drug with amino groups in the molecule such as quinine, show a comparatively good correlation between the relative response electric potential (mV) of channels 1 or 2 of the taste sensor, which contain negatively charged membranes, and the bitterness as determined by human gustatory sensations tests.

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 sparfoloxacin, with threshold concentration being 100 μg/ml. Generally the taste evaluation involves the objective or analytical method and subjective or hedonic method effect.

REFERENCES
2. Vummaneni Vishnumurthy, Nagpal Dheeraj in “Taste masking technologies: An overview and recent updates”.
3. Sharma Vijay, Chopra Himanshu in “Role of taste and taste masking of bitter drugs in pharmaceutical industries”.


Correspondence Address:
ANKITA SRIVASTAVA
Ankita Srivastava D/O Vinod Kumar Srivastava
Brahmpuri, Balasaur, Devi road, Kotdwara, Dist: Pauri Garhwal
Uttarakhand, Pin code 246149.
Tel: 9411124504
Email: ankitampharm@gmail.com