A REVIEW: TASTE MASKING TECHNIQUES IN PHARMACEUTICALS

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ABSTRACT
Taste is an important parameter in administering drugs orally and is a critical factor to be considered while formulating orodispensible, melt in mouth, buccal tablet and other formulations which come in contact with taste buds. Good flavor and texture are found to significantly affect sell of the product. Undesirable taste is one of the important formulation problems encountered with most of the drugs. Taste masking technologies offer a great scope for invention and patents. Several approaches like adding flavors and sweeteners, use of lipoproteins for inhibiting bitterness, numbing of taste buds, coating of drug with inert agents, microencapsulation, multiple emulsion, viscosity modifiers, vesicles and liposomes, prodrug formation, salt formation, formation of inclusion and molecular complexes, solid dispersion system and application of ion exchange resins have been tried by the formulators to mask the unpleasant taste of the bitter drugs. The present review attempts to give a brief account of different technologies of taste masking with respect to dosage form and novel methods of evaluation of taste masking effect.

Keywords: Taste masking, Bitter drugs, Masking methods, Evaluation.

INTRODUCTION
Taste masking technology

Taste is an important parameter in administering drugs orally. Undesirable taste is one of the important formulation problems that are encountered with many drugs. Administration of bitter drugs orally with acceptable level of palatability is a key issue for health care providers. Proven methods for bitterness reduction and inhibition have resulted in improved palatability of oral pharmaceuticals. Several oral pharmaceuticals, numerous food and beverage products, and bulking agents have unpleasant, bitter-tasting components. The methods most commonly involved for achieving taste masking include various chemical and physical methods that prevent the drug substance from interaction with taste buds.

Factors affecting selection of taste masking technology

Different taste masking technologies have been used to address the problem of patient compliance. With aggressively bad tasting medicaments even a little exposure is
sufficient to perceive the bad taste. Conventional taste masking techniques such as the use of sweeteners, amino acids and flavoring agents alone are often inadequate in masking the taste of highly bitter drugs such as quinine, celecoxib, etoricoxib, antibiotics like levofloxacin, Sweeteners could not achieve taste masking of oral formulation of ibuprofen due to its dominating taste.\cite{3}

An ideal taste masking process and formulation and characterization should have the following properties.\cite{4}

1) Involve least number of equipments and processing steps.
2) Require minimum number of excipients for an optimum formulation
3) No adverse effect on drug bioavailability
4) Require excipients that are economical and easily available.
5) Least manufacturing cost.
6) Can be carried out at room temperature.
7) Require excipients that have high margin of safety
8) Rapid and easy to prepare.

TASTE MASKING TECHNOLOGIES

Various methods are available to physically mask the undesirable taste of drugs, some of which are described below:

1. Taste masking with flavors, sweeteners, and amino acids
2. Polymer coating of drug:
3. Formation of inclusion complexes:
4. Ion exchange resin complexes:
5. Solid dispersion
6. Microencapsulation
7. Mass extrusion
8. Multiple Emulsions
9. Development of Liposome
10. Prodrug concept
11. Taste masking by spraydrying technique
12. Taste masking by adsorption
13. Taste Masking with Lipophilic Vehicles like lipids and lecithins
1. Taste masking with flavors, sweeteners, and amino acids

This technique is the foremost and the simplest approach for taste masking, especially in the case of pediatric formulations, chewable tablets, and liquid formulations. But this approach is not very successful for highly bitter and highly water soluble drugs.

The materials for taste masking purpose have often been classified depending upon the basic taste that is masked. Natural products include fruit juices, aromatic oils such as peppermint and lemon oils, herbs, spices and distilled fractions of these. The list of flavouring agents are shown in (table no.1). They are available as concentrated extracts, alcoholic or aqueous solutions, syrups or spirit.

Clove oil and calcium carbonate, which has been found to be particularly useful to mask the unpalatable active in formulations which are intended to be chewed or dissolve in mouth prior to ingestion in solution. Aspartame and sodium saccharine are the sweeteners used to mask the bitter taste of drugs. list of sweeteners are shown in (table no. 2) Monosodium glycyrrhizinate together with flavors has been used to mask the bitter taste of guaifenesin.

<table>
<thead>
<tr>
<th></th>
<th>Basis of Choosing a Flavor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juices – Raspberry</td>
<td>Complementary to existing flavor of the drug</td>
</tr>
<tr>
<td>Extracts – Liquorice</td>
<td>Known popularity of particular flavors</td>
</tr>
<tr>
<td>Spirits - Lemon &amp; Orange</td>
<td>Age of patients</td>
</tr>
<tr>
<td>Aromatic Oils – Peppermint &amp; Lemon.</td>
<td>Allergy</td>
</tr>
</tbody>
</table>

**TABLE 1: LIST OF FLAVOURING AGENTS**

Use of sweeteners

- Complement flavors associated with sweetness.
- Soothing effect on the membranes of the throat.
TABLE 2: LIST OF SWEETNERS

<table>
<thead>
<tr>
<th>Natural Sweetener</th>
<th>Artificial sweetener</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucrose, glucose, fructose</td>
<td>Saccharin, Saccharin sodium</td>
</tr>
<tr>
<td>Sorbitol, mannitol, glycerol</td>
<td>Aspartame</td>
</tr>
<tr>
<td>Honey, liquorice</td>
<td>Artificial Sweetener</td>
</tr>
</tbody>
</table>

2. Polymer coating of drug:

One of the most important factors to be considered in taste masking by coating is selection of coating polymers. By Coating one avoid the contact of bitter drug by preventing release of bitter drug in oral cavity. Proper selection of coating material will mask taste of bitter drug completely without affecting drug release profile.[5] These coating agents simply provide a physical barrier over the drug particles. Various inert coating agents are shown in (Table no.3) like starch; povidone, gelatin, methylcellulose, ethyl cellulose etc. are used for coating drug particles. Any nontoxic polymer that is insoluble at pH 7.4 and soluble at acidic pH, would be an acceptable alternative for taste masking. Taste masking of ibuprofen has been successfully achieved by using the air suspension coating technique to form microcapsules, which comprises a pharmaceutical core of a crystalline ibuprofen and methacrylic acid copolymer coating that provides chewable taste masked characteristics. One of the most efficient method of drug particle coating is the fluidized bed processor. In this approach powder's as fine as 50 μm, are fluidized in expansion chamber by means of heated, high velocity air and the drug particles are coated with a coating solution introduced usually from the top as spray through nozzle. The coated granules are dried with warm air.

TABLE 3: TASTE MASKING BY POLYMER COATING

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Drugs</th>
<th>Technique</th>
<th>Polymer Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pinaverium bromide</td>
<td>coating</td>
<td>Cellulose or shellac</td>
</tr>
<tr>
<td>2</td>
<td>Propantheline bromide</td>
<td>coating</td>
<td>L-HPC,EC</td>
</tr>
<tr>
<td>3</td>
<td>Ibuprofen</td>
<td>Air-suspension coating</td>
<td>Methacrylic acid co-polymer(Eudragit)</td>
</tr>
<tr>
<td>4</td>
<td>Triprolidine HCL</td>
<td>Dispersion coating</td>
<td>HPMC</td>
</tr>
<tr>
<td>5</td>
<td>Dimenhydrinate</td>
<td>-</td>
<td>Eudragit or CMC</td>
</tr>
</tbody>
</table>
3. Formation of inclusion complexes:

In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent i.e., the host molecule forming a stable complex. The complexing agent is capable of masking the bitter taste of the drug shown in (Table no.4) 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 Waals forces are mainly involved in inclusion complexes. Cyclodextrin is most commonly used complexing agent as well as channeling agent to form inclusion complex formation for the taste masking of bitter taste of the drugs either by decreasing its solubility or by decreasing exposure of drug particle to taste buds there.

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>ComplexingAgent</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benexate Hydrochloride</td>
<td>Cyclodextrin</td>
<td>Granules</td>
</tr>
<tr>
<td>Carbepentane citrate</td>
<td>Cyclodextrin</td>
<td>Oral liquid</td>
</tr>
<tr>
<td>Chloroquine Phosphate</td>
<td>Tannic acid</td>
<td>Syrup</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>Eudragit S 100</td>
<td>Chewable Tablet</td>
</tr>
<tr>
<td>Gymnema Sylvestra</td>
<td>Chitosan</td>
<td>Oral liquid</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Hydroxy propyl-β-cyclodextrin</td>
<td>Solution</td>
</tr>
</tbody>
</table>

**TABLE 4: TASTE MASKING BY COMPLEXING AGENTS**
4. Ion exchange resin complexes

One of the popular approaches in the taste masking of bitter drugs is based on IER. IER are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium.\(^9\) Synthetic ion exchange resin have been used in pharmacy and medicine for taste masking or controlled release of drug as early as 1950.\(^10\) Bitter tasting drugs can be absorbed onto ion exchange resins, thus effectively removing them from solution during the transit through the mouth, at salivary pH 6.7, remains in intact form making the drug unavailable for the taste sensation. Various studies have revealed that ion exchange resins are equally suitable for drug delivery technology.\(^11\)

The adsorption of bitter drugs onto synthetic ion exchange resins to achieve taste coverage has been well documented. Ion exchange resins like Amberlite CG 50 was used for taste masking of psedoephedrin in the chewable Rondec decongestant tablet. Antibacterial belonging to quinolone category like ciprofloxacin was loaded on cation exchanger and administered to animals. Some bitter drugs whose taste has been masked by using ion exchange resin are listed in the (Table no.4.)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ion exchange resin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfloxacin</td>
<td>Indion 204 (weak cation exchange resin)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Indion 234 (weak cation exchange resin)</td>
</tr>
<tr>
<td>Roxithromycin</td>
<td>Indion 204 (weak cation exchange resin)</td>
</tr>
<tr>
<td>Chloroquine phosphate</td>
<td>Indion 234 (weak cation exchange resin)</td>
</tr>
</tbody>
</table>

Charged drugs are normally loaded on to ion exchange resins by two methods, viz, column method and batch method.

**Column method**

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

**Batch method**
In this method the drug solution is agitated with a quantity of resin particles until equilibrium is established. The reaction involved during complexation of drug with resin may be indicated as follows:

\[
\text{Re COO} \ H^+ \ + \ \text{Basic drug}^+ \ \rightarrow \ \text{Re COO} \ \text{Drug}^{++} \ H^+ \\
\text{Re N(CH3)}^+ \text{Cl}^- \ + \ \text{Acidic drug} \ \rightarrow \ \text{Re N(CH3)}^+ \text{Drug} + \text{Cl}^-
\]

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. Properties of Pharmaceutical grade resins are shown in (Table No.6).

**TABLE 6: PROPERTIES OF PHARMACEUTICAL GRADE RESINS**

<table>
<thead>
<tr>
<th>Pharmaceutical Grade Resins PRODUCT NAME</th>
<th>INDION 204</th>
<th>INDION 214</th>
<th>INDION 224</th>
<th>INDION 234</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applications</td>
<td>Taste masking of bitter drugs such as Norfloxacin, Ofloxacin</td>
<td>Taste masking of bitter drugs such as Azithromycin</td>
<td>Sustained release agent in drug formulations</td>
<td>Taste masking of bitter drugs such as Ciprofloxacin, Chloroquin phosphate</td>
</tr>
<tr>
<td>Matrix type</td>
<td>Crosslinked polyacrylic</td>
<td>Crosslinked polyacrylic</td>
<td>Styrene DVB</td>
<td>Crosslinked polyacrylic</td>
</tr>
<tr>
<td>Functional Group</td>
<td>-coo</td>
<td>-coo</td>
<td>-SO₃⁻</td>
<td>-coo</td>
</tr>
<tr>
<td>Standard Ionic Form</td>
<td>H⁺</td>
<td>H⁺</td>
<td>H⁺</td>
<td>K⁺</td>
</tr>
<tr>
<td>Particle size range, mm</td>
<td>≤0.15</td>
<td>≤0.15</td>
<td>0.2 – 1.2</td>
<td>≤0.15</td>
</tr>
<tr>
<td>% Moisture</td>
<td>≤5</td>
<td>≤5</td>
<td>≤3</td>
<td>≤10</td>
</tr>
<tr>
<td>Total Exchange Capacity meq/g, dry</td>
<td>10.0</td>
<td>10.0</td>
<td>4.8</td>
<td>NA</td>
</tr>
</tbody>
</table>

5. 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.\(^{[12]}\) Solid dispersion can also be prepared by co precipitatemethod for that preparation obtained by solvent method such as coprecipitate of sulphasalazine and...
povidone. In this insoluble matrices or blend matrices may be used to mask the taste of drugs.[13]

Various approaches for preparation of solid dispersion are described below:

i) Melting method

In this method, the drug or drug mixture and a carrier are melted together by heating. The melted mixture is cooled & solidified rapidly in an ice bath with vigorous stirring. The final solid mass is crushed & pulverised.[14]

ii) Solvent method

In this method, the active drug and carrier are dissolved in a common solvent, followed by solvent evaporation and recovery of the solid dispersion.

iii) Melting solvent method

In this method drug in solutions is incorporated into molten mass of polyethylene glycol at a temperature 70°C without removing the solvent.[15]

6. Microencapsulation

This process can be used for masking of bitter tasting drugs microencapsulating drug particles with various coating agents. Coating agents employed includes gelatin, povidone, HPMC, ethyl cellulose, Bees wax, carnauba wax, acrylics and shellac.[16]

In this method bitter drugs are first encapsulated to give free flowing micro capsules which are then blended with excipients and compressed into tablet. Methods used to prepare microencapsules are air suspension, coacervation, phase separation, spray drying and cogelling, pan coating, solvent evaporation and multiorifice centrifugation method.[17]

7. Mass extrusion

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.[18]

8. Multiple Emulsions

A novel technique for taste masking of drugs employing multiple emulsions has been prepared by dissolving drug in the inner aqueous phase of w/o/w emulsion under
conditions of good shelf stability. The formulation is designed to release the drug through the oil phase in the presence of gastrointestinal fluid.[19]

9. Development of Liposome

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 phosphatidyl choline masked the bitter taste of chloroquine phosphate in HEPES (N-2-hydroxyethylpiperazine-N’-2-ethane sulfonic acid) buffer at pH 7.2.[20]

10. Prodrug concept

A prodrug is chemically modified inert drug precursor which upon biotransformation liberates the pharmaceutically active parent compound. Examples of drug with improved taste are given below in (Table no.7)

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Parent drug</th>
<th>Prodrug with improved taste</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chloramphenicol</td>
<td>Palmitate ester</td>
</tr>
<tr>
<td>2</td>
<td>Clindamycin</td>
<td>Palmitate ester</td>
</tr>
<tr>
<td>3</td>
<td>Triamcinolone</td>
<td>Diacetate est</td>
</tr>
</tbody>
</table>

11. Taste masking by spray drying technique

In the present investigation, bitter taste of drug is masked by preparing microparticles of drug with certain hydrophilic polymers such as Hydroxypropyl methylcellulose (HPMC) and polyvinyl pyrrolidone (PVP) by using spray drying technique.[21]

12. Taste masking by adsorption

Adsorbate of bitter tasting drug can be considered as the less saliva soluble versions of these drugs. Adsorption involves preparing a solution of the drug and mixing it with an insoluble powder that will adsorb the drug, removing the solvent, drying the resultant powder, and then using this dried adsorbates in the preparation of the final dosage form. Many substrates like veegum, bentonite, silica gel and silicates can be used for the preparation of adsorbate of bitter drugs.

Loperamide and phenylpropanolamine have been adsorbed on magnesium aluminium silicates also known as Veegum F to prepare bitter taste masked suspension of these drugs.[22]
13. Taste Masking with Lipophilic Vehicles like lipids and lecithins

Oils, surfactants, polyalcohols, and lipids effectively increase the viscosity in the mouth and coat the taste buds, and therefore they are potential taste masking agents. Acetaminophen granules are sprayed with molten stearyl stearate, mixed with suitable tablet excipients, and incorporated into a taste masked, chewable tablet formulation. Formulations with a large excess of lecithin or lecithin-like substances are claimed to control bitter taste in pharmaceuticals. Magnesium aluminum silicate with soybean lecithin is used to mask the unpleasant taste of talampicillin HCl.

Techniques Employed for Taste Masking of Different Dosage Forms Tablets

Most of the tablets can be effectively masked for their taste by applying inert polymer coatings that prevent the interaction of the drug substance with the taste buds. Nevertheless, attempts have been made time and again by several workers to investigate and explore the use of newer materials in bad taste abatement and good taste enhancement.

Granules / Powders

Granules for reconstituting as liquids (e.g. sachets, sprinkle capsules & powders) hold a high share of pediatric and geriatric market. A large number of patents on the topic highlight the significance of the same. Thus taste masking of granules becomes an important priority in product development and varied technologies and methodologies exist for the same as illustrated below. Hayward et al. have reported a granular composition for taste masking comprising of drug core of a NSAID and methacrylate ester copolymers as coating agents for taste masking. The method comprises of coating the drug cores with separate layers of aqueous dispersions of the copolymers. Granules of the invention could be used in the preparation of chewable tablets, which had good palatability and bioavailability.

Liquids

They present a major challenge in taste masking because the majority of pediatric preparations are syrups and suspensions although, the before mentioned methodologies have also had been used for improving liquid taste and few patents in this area are worth mentioning. Nakona et al. masked the bitter taste of vitamin B1 derivatives such as dicethimine by formulating with menthol and or polyoxyethylene, polyoxypropylene for
formulating oral liquids. Meyer et al. used prolamine, applied as single coating in weight ratio 5% to 100% relative to active substance being coated resulting the production of a liquid suspension which effectively masked the taste of orally administered drugs which are extremely bitter. Prolamine coating does not restrict the immediate bioavailability of the active substance. Prolamine coating is effective in masking the taste of antibiotics, vitamins, dietary fibers, analgesic, enzymes, and hormones.

**EVALUATION TECHNIQUES**

**Sensory evaluation**

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

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

**Panel Testing**

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

**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.

**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.\[26\]

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 \textit{in vivo}. This technique has been applied to evaluate the taste masked granules of sparfloxacin, with threshold concentration being 100 \(\mu\)g/ml.\[27\]

Recent approaches and development of taste masking

Development a taste masked microcapsules composition for oral administration of a drug. The composition compromise microcapsules of a drugs and substantially water-insoluble polymeric material, typically a cellulose polymer (ethyl cellulose). Taste masking was done phase separation coacervation, emulsion solvent diffusion technique in which the drug was coated with relatively high level of polymeric material. These high coating levels gives rise to effective taste masking, while the never less allowing targeted release of drug, so the drug was release shortly after passages through the mouth microcapsules were evaluated for flow, color, odor, mouth feel/grittiness, taste-masking, bitterness, after taste and overall acceptance. The microcapsules composition may be incorporated into any number of pharmaceutical formulations, including chewable tablets, effervescent tablet powders, liquid dispersion dispersible tablet. Dispersible tablet: These are tablets that disintegrate within three minutes to form a suspension with a pleasant taste when placed in a small amount of water, e.g. in a tablespoonful or a glass of water. However, they can also be placed directly on the tongue and sucked.\[28\]

Advantages of dispersible tablets: They are ease to swallow, so they are particularly
suitable both for elderly persons with swallowing difficulties and for children.\textsuperscript{[29]} They have quicker onset of action. Certain dispersible tablet’s can also be divided. The bitter taste of the active substances must be masked in advance. Owing to the number of possible applications, the patient compliance is improved.

CONCLUSION

Taste masking of bitter drugs has been a challenge to the scientist. We have made an attempt to describe various methods, which could be suitable for taste masking of bitter drugs. There are number of technologies available which effectively mask the objectionable taste of drugs but require skill ful application which does not affect the bioavailability of drug. With application of these techniques and proper evaluation of taste masking effect one can improve product preference to a large extent. Moreover, the development of taste masking methodology requires great technical skill, and the need for massive experimentation.

REFERENCES


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