ROLE OF TASTE AND TASTE MASKING OF BITTER DRUGS IN PHARMACEUTICAL INDUSTRIES- AN OVERVIEW

VIJAY SHARMA1, HIMANSHU CHOPRA2
Faculty of Pharmacy, P.R.C., Prist University Thanjavur-614904 (T.N.) India, Department of Pharmacy, G.R.D. (P.G.) I.M.T. Dehradun (U.K.) Email: vijaysrampur@gmail.com

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ABSTRACTS

Acceptability of any drug dosage form mainly depends over its taste i.e. mouth feel. Drug molecule interacts with taste receptor on the tongue to give bitter, sweet or other taste sensation, when they dissolve in saliva. This sensation of taste is the result of signal transduction from the receptor organs for taste, commonly known as taste buds. Now a days most of the potent drugs that may be cardiac, analgesics, anti inflammatory, anti tubercular, antihelmints , antibacterial,anticoagulants, anti epileptics, antimalarials, anti neoplastics, anti thyroids, antiprotozoal, diuretics, histamine receptor antagonists, nutritional agents, opioids analgesics, oral vaccines and sex hormones , most of them are bitter in taste. So it becomes necessary to develop such a dosage for that must be acceptable in taste to patient especially in case of children or geriatrics.

To overcome this problem so many techniques are available to mask the bitter taste of drugs. These techniques are not only serves as to mask the taste of drug as well as to enhance the bioavailability of drug dosage form. Commonly used techniques that are adopted for large scale production of pharmaceutical dosage form are use of flavors, coating of drug particle with inert materials, by formation of inclusion complexes, by Molecular complexes of drug with other chemicals, Microencapsulation, Multiple Emulsions, Prodrugs using liposomes, Dispersion coating and Ion Exchange Resin approach.

Keywords: Taste, Taste buds, Taste Masking, Drugs, and Polymers.

INTRODUCTION

Whenever we join somebody on dining table and those bodies ask about the taste of any food, that time we told any one out of four taste that may be sweet, sour, bitter or salty. Although it is a matter of dispute over the type of taste but generally these four are considered most. Now point is that how we justify about the taste of any food. This all is done by our tongue. Our tongue having so many cell located over it that helps in justifying the taste, called as taste buds. In 1908 Japanese researcher KIKUAE IKEDA found a new fifth taste in glutamate that is called UMAMI, mean meaty.1-4

TASTE BUDS

Taste buds are small sense organ in most vertebrates, helps in the detection of taste. Hence a group of cells, found especially on the tongue. Taste buds have been identified on the soft palate, pharynx, epiglottis, which allows different types of taste to be recognized,1-7

Salty taste (edge, upper portion)
The salty taste is one among the four taste receptors of tongue. They are located on the edge and upper front portion of the tongue.1-2

Sweet taste (tip)
The sweet taste is one among the four taste receptors in the tongue. They are found on the tip of the tongue.1-2

Sour taste (along sides in back)
The sour taste is also one of the four taste receptors of the tongue. They occur at sides of the tongue and are stimulated mainly by acids.1-2

Bitter taste (back)
The bitter taste is the last and one of the four taste receptors in the tongue. That is located toward the back of the tongue. It is stimulated by a variety of chemical substances, most of which are organic compounds, although some inorganic compounds such as magnesium and calcium also produce bitter sensations.1-2

Working of taste buds1-4

Taste buds works by transmitting information about different kind of taste to brain via nerve fibers. Taste buds for all four type 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, epiglottis e. The tongue, soft palate and epiglottis consists of taste buds, that allow human to recognize different tastes in food a they eat. The taste buds are chemos receptor, meaning that they transmit chemical signals in food into electrical signals. These signals travel to the brain via nervous system to experience sensation of taste.

It is to be noted that taste buds in fishes are distributed over the entire surface of the body to provide information about surroundings.1-4

Effect of age on taste buds5-7

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. Researches have been proved that that smoking and eating of scalding food may damage to taste buds. This lack of taste may lead to loss of appetite and poor nutrition.

Taste is a type of medium to experience the world of tastes for infants and young children. It is seen that children are more sensitive to certain taste than any adults. but because taste can be subjective, the mechanism that causes taste sensitivity in youngsters can be difficult to analyze.

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.1-4

Methods to test taste buds6-7

To conduct this experiment we requires followings-

*Food color

Procedure

1. With help of cotton put food color over tip of your tongue
2. Put reinforcement ring over tongue.

3. Start counting of pink dots inside the ring by using magnifying glass.

These pink dots are fungi form papillae. These are having property of not to take up the food coloring. These papillae are tiny bumps like on our tongue i.e. house your taste buds more the number of papillae means more the sensitivity against the taste. If any person having less than 15 papillae on average called as non taster while those having more than 30 called as super taster.6,7

Pharmaceutical approaches used to mask the taste of bitter drugs

Use of flavours and sweeteners 8,9

Materials available for taste masking can be classified according to basic taste that is to be masked. Flavoring agents can be natural or synthetic in nature. Natural flavors are as Peppermint, Lemon oil; Clove, Balsam, funnel and other distilled fractions. These are available as concentrated extracts, alcoholic or aqueous solutions, syrups or spirit. many compositions show effective taste masking abilities with improved flavor like alkaline earth oxides, an alkaline hydroxide or alkaline earth hydroxide. Another composition consisting phosphorylated amino acid such as phosphotyrosine, phosphoserine, and phosphothreonine and mixtures. Anethole is the flavor effectively masked bitter taste as well as the after taste of zinc, which is use in treatment of the common cold. 8

Clove oil and calcium carbonate found to be useful to mask the unpalatable active drugs in formulations which are intended to be chewed or in formulation of mouth dissolving tablet. Aspartame and sodium saccharine are the sweeteners used to mask the bitter taste of drugs.9

Table 1

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Author</th>
<th>Drug</th>
<th>Flavor</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Gohel M,10</td>
<td>Nimesulide</td>
<td>Camphor</td>
<td>Camphor significantly masked the taste of tablet with sufficient strength, friability, disintegration and dissolution.</td>
</tr>
<tr>
<td>2.</td>
<td>Dandagi 11</td>
<td>Ofloxacin</td>
<td>Aspartame</td>
<td>Aspartame significantly masked the taste of tablet</td>
</tr>
</tbody>
</table>

Coating of drugs using a suitable polymer

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. Taste masking of ibuprofen done by using the air suspension coating technique to form micro capsules, which comprises a pharmaceutical core of a crystalline Ibuprofen and meth acryl acid copolymer coating that helps in formulation of chewable taste masked tablet. Coating agents are used for coating drug particles like starch; povidone, gelatin, methy cellulose, ethyl cellulose, hydroxyl propyl methyl cellulose etc. 12

Shellac is a natural polymer, which is used as enteric coating material in pharmaceutical applications, provide moisture protective and taste masking coating. 13

Coating of drug by spraying 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. 14

Table 2

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Author</th>
<th>Drug</th>
<th>Polymer</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Hiroya,12</td>
<td>Indeloxazine hydrochloride</td>
<td>mixture comprising hydrogenated oil and surfactants</td>
<td>Powders of Indeloxazine hydrochloride without this bitter taste, microparticles (median diameter, 130 µm) of IDX were coated to mask the taste.</td>
</tr>
<tr>
<td>2.</td>
<td>Shirai15</td>
<td>Sparfloxacin</td>
<td>Low substituted hydroxypropyl cellulose, ethyl cellulose</td>
<td>Degree of Taste masking increases by ethyl cellulose And HPMC ratio. Complete taste masking was done EC: HPMC (4/2)</td>
</tr>
</tbody>
</table>

Taste masking by spray-drying technique

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Table 3

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<tr>
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<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.</td>
<td>Shreenivas S.A., 18</td>
<td>Ondensetron hydrochloride</td>
<td>Chitosan, Methocel E15 LV, and Eudragit E100</td>
<td>Taste-masked microparticles of intensely bitter drug ondensetron hydrochloride (OSH) with complete taste masking.</td>
</tr>
<tr>
<td>3.</td>
<td>Shirai19</td>
<td>Sparfloxacin</td>
<td>Low substituted hydroxypropyl cellulose, ethyl cellulose</td>
<td>Degree of Taste masking increases by ethyl cellulose And HPMC. Complete taste masking was done EC: HPMC (4/2)</td>
</tr>
</tbody>
</table>

Complex formation with ion exchange resin

Another approach in development of taste masking is based on ion exchange resin used for large scale production. Ion exchange resins are solid and insoluble high molecular weight poly electrolytes. These ion exchange resins can change their mobile ions of equal charge with surrounding media. The resulting ion exchange is reversible and stechiometric with displacement of one ionic species by another.15

Resin like Tulsion 335 (Polarflex), Indion 204 & 234 found as a commercial resin for taste masking of several drugs. Indion 204 and...
234 are weak cation exchange resin, used for taste masking of norfloxacin and ciprofloxacin respectively. Tulsion 335 is being used for preparation of nicotine polacrilex and vit B12 loading/stabilization. 

Strong cation exchange resin (viz. Amberlite IRP69) are being used to improve the physicochemical properties of ranitidine hydrochloride such as taste and bulk properties and to sustain dissolution rate. As these are high molecular weight and water insoluble resins are not absorbed by the body and are inert in nature. The adsorption of bitter drugs onto synthetic ion exchange resin like amberlite G50 was used for taste masking of pseudoephedrine in the chewable decongestant tablet. 

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Author</th>
<th>Drug</th>
<th>Ion exchange resin</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Madgulkar, A. R.</td>
<td>Tramadol HCl</td>
<td>Tulsion335</td>
<td>Taste-masked tablet formulated of significant mechanical strength that showed fast disintegration.</td>
</tr>
<tr>
<td>2</td>
<td>Rao C.G.G.</td>
<td>Quinine sulphate</td>
<td>Indion 234</td>
<td>The taste masked suspension on release studies showed complete drug release within 20 min.</td>
</tr>
<tr>
<td>3</td>
<td>Bhise</td>
<td>Diphenhydramine Hydrochloride</td>
<td>Indion 234</td>
<td>Taste masked tablet was formulated with sufficient strength, friability, disintegration and dissolution.</td>
</tr>
<tr>
<td>4</td>
<td>Cotterill</td>
<td>Levamisole</td>
<td>Amberlite IRP-69</td>
<td>Levamisole Amberlite IRP-69 resinate tablet was stable in mouth and release drug in acidic environment of stomach (93%).</td>
</tr>
<tr>
<td>5</td>
<td>Bhelekar</td>
<td>Ranitidine HCl</td>
<td>Indion 234</td>
<td>Stable Ranitidine HCl Indion complex shows effective drug loading at drug resin ratio 1:1.5 and temperature did not affect the complexation process.</td>
</tr>
<tr>
<td>6</td>
<td>Pisal S.</td>
<td>Ciprofloxacin</td>
<td>Indion234</td>
<td>The taste masked tablet on release studies showed complete drug release within 30 min.</td>
</tr>
</tbody>
</table>

**By inclusion complex formation**

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. 

<table>
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<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sanghavi N. M</td>
<td>Terfenadine</td>
<td>B-cyclodextrin</td>
<td>A palatable syrup of terfenadine-cyclodextrin complex was formulated.</td>
</tr>
</tbody>
</table>

**By forming solid dispersion**

Solid dispersion defined as dispersion of more active ingredients in an inert carrier or matrix at solid state prepared by fusion solvent method. Solid dispersion can also be prepared by co-precipitate method 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. 

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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Shah T.J.33</td>
<td>Rofecoxib (RXB)</td>
<td>Poloxamer 188</td>
<td>The melting method was used to prepare solid dispersions and MDT was formulated.</td>
</tr>
<tr>
<td>2</td>
<td>Punit Shah .34</td>
<td>Artemether</td>
<td>Mono Amino Glycyrrh- yzinate Pentahydrate (GLY)</td>
<td>Results conclusively demonstrated successful masking of taste and rapid disintegration of the formulated tablets in the oral cavity with improved dissolution.</td>
</tr>
</tbody>
</table>

**Microencapsulation technique**

Microencapsulation is a process of applying relatively thin coating to small particles of solid, droplets of liquid and dispersion. This is the method being widely used in Pharma industries to mask that taste of bitter drugs as well as bioavailability. Coating agents employed in microencapsulation are gelatin, povidone HPMC, ethylcellulose, carnauba wax, acrylics and shellac. 

<table>
<thead>
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<th>Polymer</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Al-omran37</td>
<td>Diclofenac sodium</td>
<td>Ethyl cellulose, Diethyl phthalate and polyethylene glycol</td>
<td>The optimum solvent, and non solvent ratio required for microencapsulation was 1:2. Taste masking was affected by microcapsule core: wall ratio, presence of additive and concentration of plasticizer.</td>
</tr>
</tbody>
</table>
**By multiple emulsion preparation**

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. 

<table>
<thead>
<tr>
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<th>Polymer</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Wien T.39</td>
<td>Quinine, denatortium and propranolol</td>
<td>lipoprotein composed of phosphatidic acid (PA) and β-lactoglobulin (LG)</td>
<td>These prepared with the smallest internal droplet volume (63 μl), the initial burst release was reduced significantly, and 50% (w/w) of the loaded BB remained in the microspheres for 7 days.</td>
</tr>
</tbody>
</table>

**By liposome formation**

This is another way of masking the unpleasant taste of bitter therapeutic drugs. By incorporating them into liposomal formulation prepared from 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.

<table>
<thead>
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</tr>
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<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td>These prepared with the smallest internal droplet volume (63 μl), the initial burst release was reduced significantly, and 50% (w/w) of the loaded BB remained in the microspheres for 7 days.</td>
</tr>
</tbody>
</table>

**Prodrug approach 40**

Prodrugs are the chemically modified form of an active drug which on biotransformation gives active parent drug when administered; generally these are the ester form of active drug e.g.

<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>Tramcinolone</td>
<td>Dicarbonate ester</td>
</tr>
<tr>
<td>2</td>
<td>Clindamycin</td>
<td>Palmitate ester</td>
</tr>
<tr>
<td>3</td>
<td>Chloramphenicol</td>
<td>Palmitate ester</td>
</tr>
</tbody>
</table>

**CONCLUSION**

Taste masking of bitter drug is common in pharmaceutical industries to develop a desired palatable and to enhance the onset of action as well as bioavailability of drug. So all the above approaches not only being used to mask the bitter taste of drug as well as to enhance the solubility, onset of action as well as bioavailability of drug either by any one of above mentioned methods.

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