Taste Masking Methods and Techniques in Oral Pharmaceuticals: Current Perspectives

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ABSTRACT

Undesirable taste is one of several important formulation problems that are encountered with certain drugs. The problem of bitter and obnoxious taste of is a challenge to the pharmacist in the present scenario. Taste is an important parameter governing compliance. Several oral pharmaceuticals and bulking agents have unpleasant, bitter-tasting components. In numerous cases, the bitter taste modality is an undesirable trait of the product or formulations and can considerably affect its acceptability by consumers. Bitter characteristics found in such systems have been eliminated or minimized by various known processes, but no universally applicable technology for bitterness inhibition has ever been recognized. The desire of improved palatability in these products has prompted the development of numerous formulations with improved performance and acceptability. This paper reviews different methods are available to mask undesirable taste of the drugs, with the applications. Popular approaches in the development of taste masking are based on coating, solid dispersion system and ion exchange resin.

Keywords: Taste masking, methods, techniques, evaluation, oral pharmaceuticals

INTRODUCTION

Taste is an important parameter governing compliance. Several of the oral pharmaceuticals, numerous food and beverage products and bulking agents, have unpleasant bitter-tasting components. Masking of bitter taste of drugs is an important parameter for the improvement of patient compliance. Many techniques have been developed which have not only improved the taste of product, but also the stability of the formulation & performance of the product. In numerous cases, the bitter taste modality is an undesirable trait of the product or formulations and can considerably affect its acceptability by consumers. There are numerous pharmaceutical and OTC (Over To Counter) preparations that contain actives, which are bitter in taste. With respect to OTC preparations, such as cough and cold syrups, the bitterness of the preparation leads to lack of patient compliance. Currently, companies are developing dissolvable films as alternative-dosing mechanisms for drug actives for patients who are unable to use the traditional dosing method, i.e., tablets. In order to ensure patient compliance and to allow dissolvable films to become a viable delivery system, bitterness masking becomes essential. This article discusses the recent approaches and methodology for bitterness reduction for oral pharmaceuticals.

The problem of bitter and obnoxious taste of drug in pediatric and geriatric formulations is a challenge to the pharmacist in the present scenario. 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. This sensation is the result of signal transudation from the receptor organs for taste, commonly known as taste buds. These taste buds contain very sensitive nerve endings, which produce and transmit electrical impulses via the seventh, ninth and tenth cranial nerves to those areas of the brain, which are devoted to the perception of taste. Two approaches are commonly utilized to overcome bad taste of the drug. The first includes reduction of drug solubility in saliva, where a balance between reduced solubility and bioavailability must be achieved.

Recently, a number of novel techniques for bitterness inhibition in pediatric and geriatric formulations have been attempted. Syrups of cinnamon, orange, cherry, and raspberry can be used to mask salty and bitter tastes. However, the extent of masking is unpredictable because of complex interactions of flavor elements. Bitterness-free vitamin B oral solutions can be prepared by adding sugars, amino acids, and fruit flavors. The bitterness of zinc stearate in lozenges intended for the common cold can be masked with saccharin, anethole-β-cycloDEXTRIN complex, and magnesium stearate. Aspartame, in 0.8% wt/vol has prominence in providing bitterness reduction for 25% acetaminophen granules. Viscosity with rheological modifiers such as gums can lower the diffusion of bitter substance from saliva to the taste buds. Acetaminophen suspensions are similarly formulated with xanthum gum (0.1%-0.2%) and microcrystalline cellulose (0.6%-1%). The mentioned techniques used alone are inefficient to mask the taste of certain drugs, necessitating the use of technological advancements. A taste-masking carrier for acetaminophen comprising melting with stearyl stearate (75°C) and spraying the melt into a fluidized bed has been reported for chewable tablets. Similarly, gabapentin, an experimental drug for seizures, has improved taste when coated with gelatin followed by partially dehydrogenated soybean oil and glycerol...
monostearate. 

Cherry, Peach, Raspberry, Orange, Lemon, Lime.

metallic Grape, Marsh, Mellow, Gurana, Berries, Mints

Basic Taste
Sweet
Acid
Metallic
Bitter

Table 1: Flavoring agents for taste masking

<table>
<thead>
<tr>
<th>Basic Taste</th>
<th>Masking agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweet</td>
<td>Vanilla, Bubble gum, Grapefruit</td>
</tr>
<tr>
<td>Acid</td>
<td>Lemon, Lime, Orange, Cherry, Grapefruit</td>
</tr>
<tr>
<td>Metallic</td>
<td>Grape, Marsh, Mellow, Gurana, Berries, Mints</td>
</tr>
<tr>
<td>Bitter</td>
<td>Liquorices, Coffee, Chocolate, Mint, Grapefruit, Cherry, Peach, Raspberry, Orange, Lemon, Lime</td>
</tr>
</tbody>
</table>

Table 2: Drug & taste masking coating techniques

<table>
<thead>
<tr>
<th>Drug</th>
<th>Technique</th>
<th>Polymer used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudoephedrine (Antihistaminic)</td>
<td>Emulsion-solvent evaporation (ESE)</td>
<td>Eudragit E&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td>D-Indobufin(Inhibitor of platelet aggregation)</td>
<td>Fluidized bed drying (FBD)</td>
<td>Eudragit E-100, RS/RL Ethyl Cellulose&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td>Clarithromycin (Antibiotic)</td>
<td>Phase separation-coacervation.</td>
<td>Eudragit E-100&lt;sup&gt;30&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cefuroxime axetil(Antibiotic)</td>
<td>Emulsion-solvent evaporation (ESE)</td>
<td>Eudragit E-100,Eudragit L-100,Eudragit RL-100&lt;sup&gt;33&lt;/sup&gt;</td>
</tr>
<tr>
<td>Beclamide(Antiepileptic)</td>
<td>Phase separation-coacervation.</td>
<td>Gelatin&lt;sup&gt;33&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ranitidine (Antiulcer)</td>
<td>Emulsion-nonsolvent evaporation (ENSE)</td>
<td>PEG, Ethyl Cellulose&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td>Oxybutynin (Antihistaminic)</td>
<td>Dispersion coating</td>
<td>Eudragit E-100&lt;sup&gt;30&lt;/sup&gt;</td>
</tr>
<tr>
<td>Indeloxazine(Cerebral activator)</td>
<td>Fluidized bed drying (FBD)</td>
<td>Hydrogenated oils &amp; surfactants&lt;sup&gt;31&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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carbapentane citrate syrup was reduced to approximately 50% by preparing a 1:1 complex with cycloexdextrin. The suppression of bitter taste by cycloexdextrin was in increasing order of alpha, gamma, and beta cycloexdextrin.12.

D) Molecular complexes of drug with other chemicals
The solubility and adsorption of drug can be modified by formation of molecular complexes. Consequently lowering drug solubility through molecular complex formation can decrease the intensity of bitterness of drug. Higuchi and Pitman33 reported that caffeine forms complexes with organic acids that are less soluble than xanthane and as such can be used to decrease the bitter taste of caffeine.

E) Microencapsulation
Microencapsulation process has been defined as a means of applying relatively thin coating to small particles of solid, droplets of liquid and dispersion. This process can be used for masking of bitter tasting drugs microencapsulating drug particles with various coating agents. Coating agents employed includes gelatin, povidone, hydroxy propyl methylcellulose, ethyl cellulose, bees wax, carnauba wax, acrylics and shellac. Bitter tasting drugs can first be encapsulated to produce free flowing microcapsules, which can then be blended with other excipients and compressed into tablets. Microencapsulation can be accomplished by variety of methods including air suspension, coacervation, phase separation, spray drying and congealing, pan coating, solvent evaporation and multi-orifice centrifugation techniques.34,35

Diclofenac Sodium microcapsules were successfully prepared using a system of ethyl cellulose - toluene - petroleum ether. Tinidazole was microencapsulated within various cellulose polymers like ethyl cellulose, eudragit-L & cellulose acetate phthalate with the final aim to mask its taste without affecting its bioavailability.36

F) Ion Exchange Resin
Another popular approach in the development of taste masking is based on ion exchange resin. Ion exchange resins are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium. The resulting ion exchange is reversible and stiechiometric with the displacement of one ionic species by another.36 Synthetic ion exchange resin has been used in pharmacy and medicine for taste masking or controlled release of drug as early as.37 Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert. The long-term safety of ion exchange resins, even while ingesting large doses as in the use of cholestyramine to reduce cholesterol is established unique advantage of ion exchange resins is due to the fixed positively or negatively charged functional groups attached to water insoluble polymer backbone. 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 pseudoephedrine in the chewable Rondec decongestant tablet.38 Antibacterial belonging to quinolone category like ciprofloxacin was loaded oncation exchange and administered to animals. The taste was improved as animal accepted the material more readily binding to a cation exchange resin like Amberlite IRP-69 masked the taste of peripheral vasodilator buflomid. Manek S.P. et al.39 evaluated resins like Indion CRP 244 and CRP 254 as taste masking agents. Some bitter drugs whose taste has been masked by using ion exchange resin are listed in the (TABLE 3). Drug release from the resin depends on two factors, the ionic environment (i.e., pH electrolyte concentration) within the GIT and the properties of resin. Drug molecules attached to the resin are released by exchanging with appropriately charged in GIT, followed by diffusion of free drug molecule out of resin. The process can be depicted by the followed equation 1 & 2 for anion exchange & cation exchange respectively. Where X & Y are ionic species in the GIT.34

\[ \text{Resin} + \text{Drug} + X = \text{Resin} + \text{Drug} + Y \]  ————Equation 1

\[ \text{Resin} + \text{Drug} + Y = \text{Resin} + \text{Drug} + X \]  ————Equation 2

Ion exchange resin can be classified into four major groups

1. Strong acid cation exchange resin, e.g., Amberlite IRP-69
2. Weak acid cation exchange resin, e.g., Amberlite IRP-65
3. Strong base anion exchange resin, e.g., Amberlite IRP-276
4. Weak base anion exchange resin, e.g., Dimethylamine resin

Ion exchange resins (IER) have received considerable attention from pharmaceutical scientists because of their versatile properties as drug delivery vehicles. In past few years, IER have been extensively studied in the development of novel drug delivery system and other biomedical applications. Several ion exchange resin products for oral and parenteral administration have been developed for immediate release and sustained release purposes. Research over last few years has revealed that IER are equally suitable for drug delivery technologies, including controlled release, transdermal, nasal, topical, and taste masking.

<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>Roxithromycin</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>Chloroquine phosphate</td>
<td>Indion 234 (weak cation exchange resin)</td>
</tr>
<tr>
<td>Buflomedil</td>
<td>Amberlite IRP-69</td>
</tr>
<tr>
<td>Chloropenhenireamine maleate</td>
<td>Indion CRP-244, Indion CRP-254</td>
</tr>
<tr>
<td>Diphenhydramine HCL</td>
<td>Indion CRP-244, Indion CRP-254</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Indion 234, Cation-anion exchange resin</td>
</tr>
</tbody>
</table>

Taste Masking Agent-104 is derived from cross-linked polymer of Methacrylic acid. It has carboxylic acid functionally which is enables its use as a taste masking agent, while the cross-linked porous nature makes it its suitable as a sustain release agent. Taste Masking Rosin-134 is derived from cross-linked polymer of acrylic acid and has a K+ ionic form. Taste Masking Rosin-134 is a very high purity polymer finding use in pharmaceutical formulations for taste masking of certain drugs, particularly B-lactum antibiotic.40

G) Solid Dispersions
They are dispersions of one or more active ingredient in an inert carrier or matrix in solid state, and insoluble or bland matrices may be used to mask the taste of bitter drugs. Carriers used in solid dispersion systems include povidone, polyethylene glycols, hydroxypropyl methylcellulose, urea, mannitol and ethylcellulose. Various approaches for preparation of solid dispersion are described below.

1) Melting method In this method, the drug or drug mixture and a 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 dis-
solved in a common solvent, followed by solvent evaporation and recovery of the solid dispersion.

3) Melting-solvent method In this method the drug in solution is incorporated into a molten mass of polyethylene glycol at a temperature below 70°C without removing the solvent.

H) 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.

I) Using 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.

J) Prodrug

A Prodrug is a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent drug. Examples of drug with improved taste are given below (TABLE 4).

Table 4: Prodrugs with improved taste

<table>
<thead>
<tr>
<th>Parent drug</th>
<th>Prodrug with improved taste</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloranphenicol</td>
<td>Palmitate ester</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Palmitate ester</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Diacetate ester</td>
</tr>
</tbody>
</table>

K) Mass extrusion method (Dispersion coating)

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.

L) Formation of Salts or Derivatives

In this approach, an attempt is made to modify the chemical composition of the drug substance itself, so as to render it less soluble in saliva and thus make it less sensitive to the taste buds. Aspirin tablets can be rendered tasteless by making magnesium salt of aspirin. D-

M) Use of Amino Acids and Protein Hydrolysates

By combining amino acids or their salts with bitter drugs, it is possible to substantially reduce the bitterness. Some of the preferred amino acids include sarcosine, alanine, taurine, glutamic acid, and glycine. The taste of ampicillin improved markedly by preparing its granules with glycine and mixing them with additional quantity of glycine, sweeteners, flavors and finally compressing them into tablets.

N) Taste-masking by Viscosity Modifications

Increasing the viscosity with thickening agents such as gums or carbohydrates can lower the diffusion of bitter substances from the salivary 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 high viscosity induced by thickening agents such as polyethylene glycol and sodium carboxy methylcellulose. Surprisingly, it has been observed that the high viscosity liquid exipient base provides taste-masking benefits to such an extent that extra strength compositions can be prepared with high concentrations of bitter tasting ingredients. For example, guaifenesin, which is normally administered in doses of not more than 100 mg in 5 ml of liquid, may be administered in doses of 200mg/5 ml, without the feel of bitter taste.

II) Techniques Employed for Taste Masking of Different Dosage Forms

The drug, i.e., the active pharmaceutical ingredient is finally formulated in a suitable dosage form such as tablet, powder, liquid, etc.

A) 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 (TABLE 5).

Table 5: Taste masking of tablet

<table>
<thead>
<tr>
<th>Materials</th>
<th>Method used for preparing Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelatin, Sugar, Citric acid, Concentrated Juice, Colorants, Flavors.</td>
<td>A solid preparation of Acetaminophen was prepared using gumi base.</td>
</tr>
<tr>
<td>A series of Eudragit polymers with difference in the frequency of the ester substituents in the chemical structure. Effervescent admixture of sodium bicarbonate and citric acid encapsulated with ethyl cellulose.</td>
<td>Polymer coating was applied on the solid dosage form and evaluated for water permeability, pH solubility, and taste masking. Microcapsules were used in formulating taste masked effervescent chewable tablets of NSAID.</td>
</tr>
<tr>
<td>Sodium alginate, calcium gluconate</td>
<td>A core tablet of Ampirilose was prepared which was under coated with calcium gluconate and over coated with sodium alginate which led to the formation of a gel on the surface of the tablet that exhibited good taste masking effect.</td>
</tr>
</tbody>
</table>

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in the preparation of chewable tablets, which had good palatability and bioavailability.

Kishimoto et al.55 used mannitol and lactose in different weight ratios (1: 1.5 - 1:5) as coating materials for masking bitter taste of solid drug preparations. Yajima et al.56 in their patent have described a composition comprising of a drug with unpleasant taste of polymer solution and D-crystals of monoglycerides. Eudragit E (100 g) was dissolved in melted stearic acid monoglyceride (600 g) and then erythromycin (300 g) were added to the mixture to obtain a powder, which was again mixed with sorbitol, magnesium oxide and starch to give taste masked granules of erythromycin.

Danielson et al.57 invented a dosage form comprising granules containing the histamine receptor antagonist which are provided with taste masking coating comprising a water insoluble, water permeable methacrylate ester copolymer in which the coating is applied to the granules in an amount which provides a taste masking effect for a relatively short period during which the composition is being chewed by a patient but which allows substantially immediate release of the histamine receptor antagonist after the composition has been chewed and ingested. Kumar et al.58 provided a means and method for manufacturing palatable drug granules using a polymer having at least one free carboxyl group and poly vinyl pyrolidone.

C) Liquids

They present a major challenge in taste masking because the majority of pediatric preparations are syrups and suspensions although, the aforementioned methodologies have also been used for improving liquid taste and few patents in this area are worth mentioning. Nakona et al.59 masked the bitter taste of vitamin B1 derivatives such as dicethimine by formulating with menthol and or polyoxyethylene, polyoxypropylene for formulating oral liquids. Osugi et al.60 in their invention subjected oral liquids containing Diclofenac and its salts to heat treatment in the presence of glycine, glycerrhizinic acid or salt derivative such as dicethimine by formulating with menthol and or polyoxyethylene, polyoxypropylene for formulating oral liquids.

Meyer et al.61 used prolamine, applied as single coating in weight ratio 5% to 100% relative to active substance being coated result in 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, analgesics, enzymes, and hormones.

Pharmaceutical composition comprising polyhydric alcohol based carrier to mask the bitter taste of a drug were reported by Swaminathan et al.62 who prepared the liquid containing cimetidine, talin, peppermint oil and glycerol. Morella et al.63 invented a liquid suspension of microcapsules taste masked as a function of a polymer coating and the pH of suspended medium at which pharmaceutically active ingredients remain substantially insoluble. Yu et al.64 invented a liquid composition comprising a pharmaceutically active medicament coated with a taste masking effective amount of polymer blend of dimethylaminooethyl methacrylate and neutral methacrylic acid ester and a cellulose ester in an aqueous vehicle. The liquid composition utilizes a reverse enteric coating, which is soluble in acid pH of the stomach generally about 1-4 but relatively insoluble at the non-acidic pH of the mouth. The coating provides the rapid release and absorption of the drug, which is generally desirable in case of liquid dosage forms.

III) Evaluation of Taste Masking Effect

Sensory analysis has been used in developed countries for years to characterize flavors, odors, and fragrances. Historically expert provided formulation scientist with subjective data on the composition of one product with another. Nowadays, sensory analysis employs objective or analytical methods and subjective or hedonic method (TABLE 6). Soutakagi, et al.65 invented a multichannel taste sensor whose transducer is composed of several kinds of lipid/polymer membrane with different characteristics, which can detect taste in manner similar to human gustatory sensation. Taste information is transformed into a pattern composed of electrical signals of membrane potential of the receptor part. It was reported that suppression of bitterness of Quinine and a drug substance by sucrose could be quantified by using multi channel taste sensor. The present method can be expected to provide new automated method to measure the strength of drug substance in place of sensory evaluation.

Table 6: Evaluation of taste masking

<table>
<thead>
<tr>
<th>Subjective Method</th>
<th>Objective Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preference Test</td>
<td>Difference Test</td>
</tr>
<tr>
<td>Paired Testing</td>
<td>Paired Difference Test</td>
</tr>
<tr>
<td>Triangle Testing</td>
<td>Triangle Difference Test</td>
</tr>
<tr>
<td>Hedonic Scale</td>
<td>Duo trio Test</td>
</tr>
<tr>
<td></td>
<td>Ranking Test</td>
</tr>
<tr>
<td></td>
<td>Analytical Test</td>
</tr>
<tr>
<td></td>
<td>Flavor Profile</td>
</tr>
<tr>
<td></td>
<td>Time Intensity Test</td>
</tr>
<tr>
<td></td>
<td>Single attribute test</td>
</tr>
<tr>
<td></td>
<td>Dilution Profile</td>
</tr>
<tr>
<td></td>
<td>Statistical Test</td>
</tr>
</tbody>
</table>

Evaluation of the taste masking effect from coated microsphere can be done by determining the rate of release of the drug from the microsphere. Similarly for evaluating the taste masking effect by ion exchange resin, the drug release rate can serve as an index of the degree of masking achieved. Other methods include evaluation by a trained flavor profile panel and time intensity method in which a sample equivalent to a normal dose was held in mouth for 10 seconds. Bitterness level are recorded immediately and assigned values between 0-3.

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. The methods described in this review can be used for bench scale as well as pilot scale also. There are numbers of technologies available, which effectively mask the objectionable taste of drugs but require skillful 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.
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