



## TASTE MASKING METHODS AND AGENTS IN PHARMACEUTICAL FORMULATIONS

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### ABSTRACT

Taste is a critical factor during development of any dosage form and it is important parameter in administering drugs orally. Undesirable and particularly bitter taste is one of the important formulation problems that are encountered with many drugs. Proven methods for bitterness reduction and inhibition have resulted in improved palatability of oral pharmaceuticals. The present review explains in detail the various methods and agents used for taste-masking like, Inclusion complexation, Ion exchange resin, Coating, Granulation, Microencapsulation, Flavors, and Sweeteners, Pro-drug etc.

The review also highlights factors affecting the selection of technology for taste masking and methods for evaluation of taste.

**Key Words:** Complexation, Evaluation, Ion exchange resin, Micro-encapsulation, Taste, Taste Masking.

### INTRODUCTION

#### Taste

The taste and smell are collectively known as chemical senses. Tongue is a versatile and muscular organ which is related to taste sensation<sup>1</sup>. The four common tastes are sweet, sour, bitter, and salty. Sweet chiefly at the tip, salt on the dorsum anteriorly, sour at the sides, and bitter at the back of the tongue<sup>2</sup>. The sense of taste is mediated by group of cells called taste buds which are composed of groups of about forty columnar epithelial cells bundled together along their long axes that sample oral concentration of a large number of small molecules and report a sensation of taste to centers in the brainstem. The taste buds themselves are too small to see without a microscope, but papillae are readily observed by close inspection of the tongue's surface.

The taste sensations are -

- 1) Sweet taste- caused by some organic compound. e.g., sugar, certain carbohydrates, and alcohols.
- 2) Salty taste- caused by inorganic compounds, such as chlorides, sulphate, bromides.
- 3) Sour taste- caused by acids or acid salts. It is due to the hydrogen ion concentration upon which the acidity depends.
- 4) Bitter taste- caused by some organic compounds, such as alkaloids (strychnine and quinine), certain glucosides, and bile salts<sup>1</sup>.

#### Taste Masking

Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist. Taste masking technologies offer a great scope for invention and patents. The ideal solution to taste masking of bitter substances is the discovery of a universal inhibitor of all bitter tasting substances that does not affect the other taste modalities such as sweetness. Proven methods for bitterness reduction and inhibition have resulted in improved palatability of oral pharmaceuticals. Taste masking technology is an important factor for improving patient compliance.<sup>4</sup>

Taste masking technology includes mainly two aspects:-

1. Selection of suitable taste masking agents such as polymers, sweeteners, flavors, amino acids.
2. Selection of suitable taste masking methods.

#### METHODS AND AGENTS<sup>3</sup>

The different methods and agents for taste masking are as follows-

#### Inclusion Complexation

Inclusion complexation is a process in which 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 either by decreasing its oral solubility on ingestion or decreasing the number of drug particles exposed to the taste buds, thereby reducing the perception of bitter taste. Cyclodextrins are the most widely used complexing agent for inclusion complex formation having lipophilic inner cavities and hydrophilic inner surfaces and are capable of interacting with a large cavity of guest molecules to form inclusion complexes. They are available in three different forms like alpha, beta and gamma containing six, seven or eight units respectively. Beta-cyclodextrin is most widely used because of its ready availability and the cavity size fits in the aromatic ring present in most drug molecules<sup>7</sup>. Various methods of preparation of inclusion complexes are co-grinding, precipitation, solid dispersion, spray drying and freeze drying<sup>8</sup>.

#### Ion Exchange Resins

Ion exchange resins are high molecular weight polymers with cationic and anionic functional groups. They can exchange their mobile ions of equal charge with surrounding medium. Synthetic ion exchange resins have been used in pharmacy for taste masking from so many years.

Drugs are attached to the resin substrate to form the insoluble adsorbates or resinates through weak ionic bonds so that the drug-resin complex will not dissociate under normal salivary pH conditions. This suitably masks the unpleasant taste and odor of drugs<sup>7</sup>.

Ion exchange resins can be classified into four major groups:

1. Strong acid cation exchange resins- these resins (sulphonated styrene divinylbenzene copolymer product) functions throughout the entire pH range and can be used for masking the taste of basic drugs.
2. Weak acid cation exchange resins - these resins function at pH values above six.
3. Strong base anion exchange resins- these resins function throughout the entire pH range and these can be used for taste masking of acidic drugs.
4. Weak base anion exchange resin- these resins function well below pH seven.<sup>7</sup>

Drug-resinate can be prepared by two methods-

1. Batch process- In this method a drug solution is agitated with a quantity of resin particles until equilibrium is established.

2. Column process- In this method a highly concentrated drug solution is passed through a column of resin particles, as the reaction is equilibrium phenomenon maximum potency and efficiency is obtained by this method.

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<sup>9</sup>. Drug molecules attached to the resin are released by exchanging with appropriately charged ions in the GIT, followed by diffusion of free drug molecule out of the resins<sup>7</sup>. Drug release from the resin depends on the properties of the resin and the ionic environment within the gastrointestinal tract (GIT).

#### **Polymer Coating**

This is one of the most important and commonly used taste masking method. The coating acts as a physical barrier to the drug particles, thereby minimizing interaction between the drug and taste buds. By using the right type of coating material it is possible to completely mask the bitter taste of a bitter drug, while at the same time, not adversely affecting the intended drug release profile.

Hydrophobic polymers, lipids, sweeteners, and hydrophilic polymers are used as coating materials, either alone or in combination, as a single or multi-layer coat. Combination of pH dependant water insoluble polymers such as cellulose ether, cellulose esters, polyvinyl acetate butyrate, polyvinylpyrrolidone, hydroxymethyl cellulose are used to attain a balance between the taste and in vitro release. Acidic compounds such as citric and malic acid can be added which creates acidic environment in order to promote the release of drug in the upper intestine from the particles coated with reverse enteric polymers. Enteric coated particles with a suspension base containing osmotically active substances like sucrose can be used in addition to the buffering agents to prolong the taste making efficiency of the formulation<sup>10</sup>.

#### **Granulation**

Granulation is a less expensive, rapid process and it is easily used for taste masking of slightly bitter tasting drugs. Granulation lowers the effective surface area of the bitter substance that comes in contact with the tongue upon oral intake and thus provides effective taste masking. Dry, wet, and melt granulation techniques are used to process the mixture of bitter medicaments and sweeteners, hydrophobic polymers, lipids or waxes to prepare taste masked oral solid or liquid dosage forms<sup>10</sup>.

#### **Flavoring Agents**

Flavoring refers to a complex effect of taste, odor and feeling factors so as to make preparation more palatable. The selection of flavor depends on the taste that is to be masked. Flavors are always a combination of various components that are formulated together to give a desired flavor profile like coolants, and desensitizers. Menthol, chloroform and various salts are used as flavor adjuncts. They impart flavor and odour of their own to product and have a mild anesthetic effect on sensory receptor organs associated with taste<sup>8</sup>.

#### **Sweeteners**

Use of sweeteners is the simplest and common approach for taste masking especially in the chewable tablets, pediatric and liquid formulations. But it is not very successful for highly bitter and highly water soluble drugs. Sweeteners can be mixed with material which is prepared for further coating or may be added to the coating liquid. Artificial sweeteners are

generally being used along with taste masking methods for improving characteristics of dosage form. Cooling effect of taste masking agents such as menthol reduces the bitterness of drug<sup>7</sup>.

#### **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 polymeric material. In this method bitter drugs are first encapsulated to give free flowing micro capsules which are then blended with excipients and compressed into tablet. The only soluble portion of the drug generates the sensation of taste. Coating the active drug with a properly selected polymer film can reduce its solubility in saliva and thus taste of the drug could be masked. The coating agents used are gelatin, povidone HPMC, ethyl cellulose, wax, acrylics and shellac.<sup>9</sup> The process can be done by using techniques such as air suspension, coacervation-phase separation etc.<sup>10</sup>

#### **Pro-Drug**

Chemical modification including pro-drug design is an effective method for reducing solubility and thus improving taste. A pro-drug is chemically modified inert drug precursor which on biotransformation liberates the pharmaceutical active parent compound<sup>18</sup>.

#### **Solid Dispersion**

Solid dispersions are dispersion of one or more active ingredients in an inert carrier or matrix. Carriers used include povidone, polyethylene glycol of various molecular weights, hydroxypropylmethyl cellulose, urea, mannitol and ethyl cellulose. Specific interaction between poorly soluble drug and hydrophilic polymers can increase the solubility of the drug and similarly specific interaction between drug and hydrophobic polymers can decrease the solubility of the drug.<sup>10</sup>

#### **Viscosity Enhancers**

Suspending coated particles or microcapsules may not be efficient enough to achieve taste masking of highly bitter medicament in liquid oral suspensions. Usage of viscosity enhancers in these cases would retard the migration of dissolved medicament from the surface of the solid particles to the suspending medium. Additionally they can also decrease the contact between the bitter medicament and the taste receptors, thus improving the overall taste masking efficiency. Viscosity enhancers such as xanthum gum, microcrystalline cellulose, and sodium carboxymethyl cellulose are used in suspending vehicle to improve the taste masking efficiency.<sup>10</sup>

#### **pH Modifiers**

pH modifying agents are capable of generating a specific pH microenvironment in aqueous media that can facilitate in situ precipitation of the bitter drug substance in saliva thereby reducing the overall taste sensation for liquid dosage forms like suspension<sup>16</sup>.

#### **Adsorbates**

Adsorbates such as vegum, bentonite, silica gel and silicates 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 a delayed release of the bitter active during the transmit through the oral cavity there by achieving taste masking.<sup>10</sup>

#### **Multiple Emulsions**

Multiple emulsions are prepared by dissolving drug in the inner aqueous phase of w/o/w emulsion and stabilized by lipophilic and hydrophilic surfactants. The release of drug through oil phase takes place in gastrointestinal fluid.<sup>5</sup>

### **Salt Formation**

The bitter taste of drugs may be masked by formulating it as salt using agents like sodium bicarbonate, ascorbic acid, citric acid, and tartaric acid.

### **Taste Masking By Gelation**

Water insoluble gelation on the surface of tablet containing bitter drug can be used for taste masking. E.g. In saliva sodium alginate has the ability to form water insoluble gelation in presence of bivalent metal ions like calcium.<sup>9</sup>

### **Molecular Complexes Of Drug With Other Chemical**

The solubility and absorption of drug can be modified by the formation of molecular complexes. Lowering drug solubility through molecular complexation can decrease the intensity of bitterness.<sup>5</sup>

### **Liposome**

Another way of masking the unpleasant taste of bitter therapeutic drugs is to entrap them into liposome that are concentric bi-layered vesicles in which aqueous volume is entirely enclosed by a membranous lipid bi-layer mainly composed of natural or synthetic phospholipids. Liposomes can encapsulate both hydrophilic and lipophilic materials.<sup>5</sup>

### **Effervescent Agents**

Effervescent agents are useful and advantageous for oral administration of drugs and are used as taste masking agents for dosage forms that are not dissolved in saliva prior to administration. The formulations containing the drugs in combination with effervescent agents promote absorption in the oral cavity and mask their bitter taste.<sup>7</sup>

### **Anesthetizing Agents**

Anesthetizing agents temporarily numb the taste buds. The loss of sensation prevents perception of taste, which helps to mask the bitter taste.

## **FACTORS AFFECTING SELECTION OF TASTE MASKING TECHNOLOGY**

### **Extent Of Bitter Taste**

In case of bad tasting medicaments even a little exposure is sufficient to perceive the bad taste. Use of different technologies depends on the extent of bitterness of the drug. For Very bitter drugs simple techniques like use of sweeteners, flavors, adsorbates are not sufficient so technologies like coating, use of resins, microencapsulation, and viscosity enhancers can complement the taste masking efficiency.

### **Dose Of Active Pharmaceuticals**

Dose of a drug may dictate whether a particular formulation strategy would be suitable to achieve taste masking. In pediatric formulations, the dose is small enough so as to allow the usage of simple techniques like flavoring agents; sweeteners etc. For higher doses, technologies like coating, use of resins, microencapsulation, and Viscosity enhancers are to be used.

### **Drug Particle Shape And Size Distribution**

Particle characteristics of drug affect the taste masking process efficiency. Core materials with irregular shapes and small particle size lead to poor taste masking efficiency and varying dissolution of coated particles. Fines abrasion and variable coating thickness can lead to situations wherein the taste mask coating is compromised.

### **Dosage Forms**

It is estimated that 50% of the population have problem of swallowing tablets, especially the pediatric and geriatric population. Chewable tablets and liquid oral dosage forms have been used to address these problems. However, it is difficult to formulate some drugs in these dosage forms due to their poor palatability. For formulations which are

swallowed unchewed: capsules, coated tablets, and slowly disintegrating hard tablets have been used as preferred taste masking technologies. Chewable tablets and liquid oral formulations are preferable in case of large dose drugs for an ease of intake. Taste masking technologies sweeteners, particulate coating, microencapsulation and granulation can be used for chewable tablets and supported with technologies such as viscosity enhancers and pH modifiers to achieve taste masking in liquid oral formulations.

### **Drug Solubility**

Physicochemical properties of drug play an important role in the selection of taste masking technology, for example, ondansetron has a relatively low water solubility at higher pH, based on which a rapidly disintegrating taste masked composition of ondansetron was formulated by adding an alkalizing agent to reduce the water solubility and consequent taste perception.

### **Ionic Characteristics Of Drug**

Ionic characteristics of drugs govern the selection of ion exchange resin polymers and the suitability of drug candidate for this technology. For example, anionic polymers are good candidates for cationic drugs like donepezil hydrochloride, and the cationic polymers are choice of excipients for anionic drugs<sup>10</sup>.

## **EVALUATION OF TASTE MASKING**

The different methods used for quantitative evaluation of taste masked products are as follows-

### **Panel Tasting**

It is a psychophysical rating of gustatory stimuli. In this method a group of about 5-10 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 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 anaesthetised intraperitoneally and the glossopharyngeal nerve is then located and dissected from the surrounding tissue. It is cut proximally and connected to an AC-amplifier and electronic integrator to respectively amplify and integrate the nerve impulses. The peak height of the integrated response is then taken as magnitude of response.

### **Multichannel Taste Sensor**

This is an automated taste sensing device to detect the magnitude of bitterness of a drug substance. The device has transducer which is composed of several kinds of lipid or 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 potential of the receptor part. Different response electric potential pattern are obtained for a substance producing different taste qualities.

### **Spectrophotometric Method**

In this method 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<sup>17</sup>.

### **Affective Tasting**

Affective tasting is used to evaluate the popularity of an aroma and/or taste impression according to like or dislike.

Samples are presented in succession and the subject is told to decide how much one like or dislike the product and to mark the scales accordingly. The nature of this test is its relative sensitivity. Affective test includes different tests such as paired test, acceptance test, and just about right test<sup>15</sup>.

#### RECENT STUDIES

Madgulkar A.R. formulated and optimized a novel taste masked mouth dissolving tablet of Tramadol hydrochloride having adequate mechanical strength using ion exchange resin -Tulsion 335.<sup>11</sup>

Madgulkar A.R. developed and optimized the fast disintegrating tablet of Fexofenadine hydrochloride by wet granulation using camphor and super-disintegrants. Computer aided optimization process using three factorial design was employed to investigate the effect of these two independent variables.<sup>12</sup>

Bhalekar M. R. masked the bitter taste of Famotidine by forming an ion exchange resin complex with Indion 214 to produce a fast disintegrating tablet of Famotidine that disintegrates in mouth immediately.<sup>13</sup>

Cabera et al developed the solid dispersion of quinolone and naphthyridone carboxylic acids in an insoluble matrix to mask the taste of active ingredient which was prepared from the solution of quinolone and the natural hydrophobic polymer shellac by solvent evaporation<sup>10</sup>.

Shishu et al have worked on, "The formulation of bitter taste masked liquid oral suspension of Nalidixic acid" using microencapsulation technique.

Shagufta Khan et al have worked on, "Masking the intensely bitter taste of Ondansetron hydrochloride using Eudragit EPO and formulated rapid disintegrating tablet (RDT) of the taste-masked drug".

Bhise et al have worked on, "Taste Masking by Spray-Drying Technique". The present study investigate Ondansetron Hydrochloride microsphere prepared by using three polymers such as Chitosan, Eudragit E100 and methocel E15W and microsphere evaluated for threshold bitterness, in vitro evaluation, IR spectroscopy, drug loading, SEM, moisture content.

#### REFERENCES

1. Chatterjee C.C. Human physiology. Calcutta (India): Medical allied agency; p. 6.1-6.6.
2. <http://www.suite101.com/article.cfm/the-human-tongue-anatomy> cited on 15September 2011
3. Bansal et al. Taste masking methods:A Patent Review.Recent patents on Drug Delivery and Formulation 2009,3(1),17-28.
4. Reilly WJ. Pharmaceutical necessities in Remington. The science and practice of pharmacy. Mack Publishing Company; 2002, 1018-1020.
5. Agrawal VA, Chiddarwar AP, Mahale AM, Wakade RB. Taste abatement techniques to improve palatability of oral pharmaceuticals. International J Pharma. Research and development 2010; 7:1-10.
6. Jain M, Pareek A, Bagdi G, Aahmad D, Aahmad A. Taste masking methods for bitter drug. International J Pharm. and LifeSci. 2010; 1(6):336-339.
7. Shodhganga.inflibnet.ac.in/bitstream/10603/2316/06 chapter 201:19-3
8. Lachman L, Liberman HA, Kanig JS. The theory and practice of industrial Pharmacy. 3rd ed. Bombay (India): Varghese publishing house; 1987. p. 419-428.
9. Sharma S, Lewis S. Taste masking technologies. International J Pha. PharmSci. 2010; 2(2):6-13.
10. Zelalem A, Puri V, Kumar L, Bansal AK. Trends in Pharmaceutical Taste Masking Technologies. Recent Patents on Drug Delivery & Formulation 2009; 3:26-39.
11. Madgulkar AR, Bhalekar MR, Padalkar RR. Formulation design and optimization of novel taste masked mouth dissolving tablets of Tramadol having adequate mechanical strength. AAPS Pharm Sci 2009; 10(2),2:574-581.
12. Madgulkar AR, Bhalekar MR, Patel K. Formulation and optimization of oral disintegrating tablets of Fexofenadine hydrochloride. Indian drugs 2008; 45(10):789-797.
13. Puri D, Bhalekar M. Evaluation of oral fast disintegrating tablet of taste masked Famotidine in rat. Latin american J Pharm 2010; 29(6):948-954.
14. Bhalekar MR, Bidkar SJ, Shete TK, Madgulkar AR. Taste masking of Cefuroxime axetil by ion exchange resin complex. Latin american J Pharm 2010; 29(2):198-204.
15. Sikandar MK, Malviya R, Sharma PK. Taste masking: An important pharmaceutical technology for the improvement of organoleptic property of pharmaceutical actives. European J biological sci 2011; 3(3):67-71.
16. Deepthi P, Chowdary YA, Murthy GK, Seshagiri KB. Approaches for taste masking of bitter drugs. Journal of advances in drug research 2011; 1 (2):58-67.
17. Nanda A, Kandrapu R, Garg S. Taste masking methods for bitter drug. Indian J PharmSci 2002; 64 (1):1-10.
18. Sharma V, Chopra H. Role of taste and taste masking of bitter drugs in pharmaceutical industries. International J Pha. PharmSci 2010:14-18.