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Taste Physiology and Taste Masking of Bitter Drugs with Special Emphasis on Complexation and Inclusion Method: A Review



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ABSTRACT

Taste drives appetite and protects us from poisons. Taste is a crucial factor that determines the palatability of pharmaceutical oral dosage form and patient compliance. It also gives a unique identity to a product and thereby provides a competitive advantage to a company, especially in the case of over-the-counter products. There are several taste masking methods available, which either involve modification of bitter active pharmaceutical ingredient itself or the formulation. Some of them are coating of drug particles, by formation of inclusion complexes, molecular complexes of drugs with other chemicals, solid dispersions, melting method, microencapsulation, prodrugs, mass extrusion methods and ion exchange resins. In past few years, Ion exchange resin and Formation of Inclusion Complexes with β -Cyclodextrin Derivative have been extensively used in the drug delivery technologies included; site specific drug delivery system, Modified release dosage form, Fast dissolving tablet, clinical medicine & Biomedical application etc. This article reviews the concept of physiology, chemistry of taste, various taste masking methods available, with special importance on Complexation with Ion Exchange Resins and Formation of Inclusion Complexes with β -Cyclodextrin Derivative methods for Taste Masking.

INTRODUCTION

Tongue is responsible for taste. Different areas of tongue are responsible for different tastes like sweet, bitter, sour and salty. The sweet sensations are easily detected at the tip whereas bitterness is most readily detected at the back of the tongue. Sour sensation occurs at the side of the tongue, but salty sensations are usually detected at both the tip and at the side of the tongue. Western civilization recognizes only four basic tastes: Sweet, Sour, Salty and Bitter. The Japanese add fifth taste called Umami for monosodium glutamate. The high perception of bitterness may be an evolutionary defense mechanism that keeps us from swallowing poisons (1).

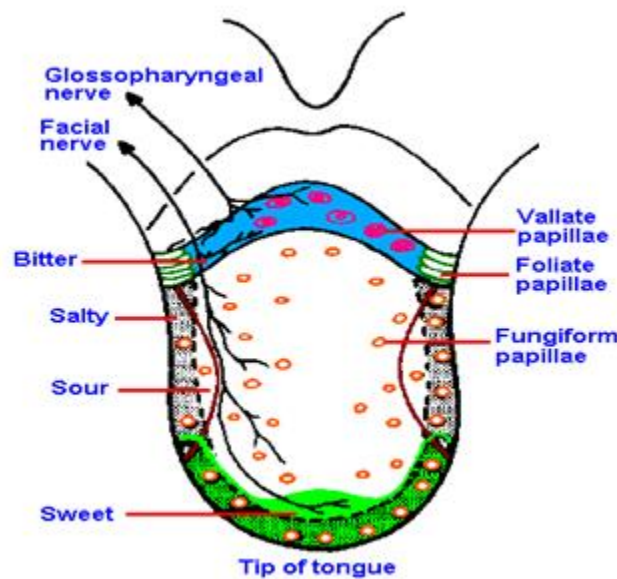


Figure 1: Physiology of the tongue

In mammals, taste buds are aggregations of 30-100 individual elongated cells, which is 50-60 microns in height and 30-70 microns in width. It is often embedded in specializations of surrounding epithelium, termed papillae. In the oral milieu the microvillar processes project through a small opening from the apex of the taste bud is called taste pore. There are afferent nerves present at the base of the taste buds. These afferent nerves invade the bud and ramify extensively. Each fiber of this nerve typically synapsing with multiple receptor cells within the taste bud (2).

Location of taste buds: The taste buds are found on three types of papillae on the tongue

- A large number of taste buds are on the wall of the trough that surrounds the circumvallate papillae, which forms 'v' line on the posterior surface of the tongue.
- Moderate numbers of taste buds are on fungiform papillae over the flat anterior surface of the tongue.
- Moderate numbers are on the foliate papillae located in the folds along the lateral surface on the tongue.
- Additional taste buds located on the palate and few on the tonsillar pillars, the epiglottis and even in the proximal esophagus (3).

Physiology of taste:

Physiologically, taste is a sensory response resulting from a chemical stimulation of taste buds on the tongue. The sense of taste is conducted to the brain by a process called taste transduction. This process begins with the interaction of tastant (i. e., food or medicine) with receptor cells in the taste buds. The tastant binds with G-protein coupled receptors in the cells, triggering the release of gustducin. Taste sensation begins when gustducin activates the effector enzymes phosphodiesterase 1a or phospholipase C β -2. The effector enzymes then change the intracellular levels of second messengers such as cyclic adenosine monophosphate (cAMP), inositol, 1,4,5-triphosphate (IP3), and diacylglycerol (DAG). The second messengers activate ion channels, including calcium channels inside the cells and sodium, potassium and calcium channels on the extracellular membrane. This ionization depolarizes the cell, causing the release of neurotransmitter that sends a nerve impulse to the brain that carries the signal of taste (4).

Chemistry of taste:

Sour:

Sour stimuli in foods, such as vinegar (acetic acid), lemon (citric acid), and apple (malic acid) are easily identifiable. All sour substances contain acids that generally ionize in aqueous solutions to produce hydrogen ions. Therefore the higher the concentration of hydrogen ions, the stronger is the sourness. Sour taste is not only dependent on hydrogen ions, but also on lipid solubility. A higher lipid solubility of acids provides for greater concentrations as taste receptors, accounting for the increase in sour sensation.

Salty:

It has been shown that cationic species are partially responsible for the salt solutions. Sodium chloride has a typical salty taste. Chlorides of potassium, ammonium and calcium have a typical salty taste, but their solutions taste differently. Most halide salts (sodium chloride, sodium bromide, potassium chloride and sodium iodide) have a dominating salty taste. Potassium bromide and ammonium bromide have a salty, bitter taste but potassium iodide is intensely bitter, which indicates that the taste sensations of salts shift to bitterness as molecular weight increases.

Sweet:

Sweet taste is produced by wide variety of compounds, many of which do not have any apparent structural similarity. The two most common sweet substances, sugars and glycerin are polyhydric alcohols containing $-CH_2OH$ groups, which contributes significantly to sweetness. Saccharin which has no $-OH$ group, is intensely sweet but has bitter aftertaste. In contrast, naturally occurring glycosides are bitter. Some amino acids, for example, glycine is sweet. The sodium and calcium salts of cyclohexyl sulfamic acid (cyclamates) and the dipeptide ester aspartame is roughly thirty times sweeter than sugar and has been used as sugar substitute.

Bitter:

A bitter taste, like sweet taste, is commonly found in a wide variety of compounds, most of which are salts of organic and inorganic compounds. Bitterness is often associated with the nitro group, and the presence of two or more nitro groups in a molecule results in a bitter taste. Structurally unrelated compounds, such as esters of aromatic acids lactones and sulfur containing aliphatic compounds exhibit bitterness (5,6).

Taste Masking:

As more than 50% of pharmaceutical products are administered orally, undesirable taste is one of the important formulation problems that can be encountered with certain drugs. Oral administration of bitter drugs with acceptable level of palatability is a key issue for health care

providers especially with pediatrics and geriatric patient. Thus, elimination or reduction of bitterness is an important issue during design of oral pharmaceutical formulations.

An ideal taste masking process and formulation should have the following properties:

- Rapid and easy to manufacture.
- Involves least number of equipment.
- Requires minimum number of excipients for an optimum formulation.
- Has no adverse effect on drug bioavailability
- Requires excipients that are economical and easily available.
- Least manufacturing cost (7).

Methods of Taste Masking:

In order to eliminate or reduce bitter taste of orally administered pharmaceuticals various techniques and strategies are adopted by pharmaceutical scientist. These strategies are classified as below-

1. Sensory Approaches:

I. Using Flavoring and Sweetening Agents (8,25)

II. Numbing of Taste Buds

2. Complexation and Adsorption:

I. Complexation with Ion Exchange Resins (26,44)

II. Formation of Inclusion Complexes with β -Cyclodextrin Derivative (45-52)

III. Wax Embedding of Drugs

3. Chemical Approaches:

I. Formation of Prodrug

II. Formation of Different Salts

4. Barrier Approaches:

- I. Using Viscosity Modifier
- II. Using Emulsions
- III. Using Liposome
- IV. Using Microspheres or Microcapsules

Complexation and Adsorption:

Complexation with cyclodextrins:

Complexation is one of several ways to favorably enhance the physiochemical properties of pharmaceutical compounds. It may loosely be defined as the reversible association of a substrate and ligand to form a new species. Although the classification of complexes is somewhat arbitrary, the differentiation is usually based on the types of interactions and species involved, e.g. metal complexes, molecular complexes, inclusion complexes and ion exchange compounds.

These complexes are formed when a “guest” molecule is partially or fully include inside a “host” molecule e.g. cyclodextrin with no covalent bonding. When inclusion complexes formed, the physicochemical parameters of the guest molecule are disguised or altered improvements in the molecule’s solubility, stability, safety, bioavailability etc., are commonly seen.

Cyclodextrin inclusion is a stoichiometric molecular phenomenon in which usually only one guest molecule interacts with the cavity of the cyclodextrin molecule to become entrapped. A variety of non-covalent forces, such as van der-walls forces, hydrophobic interactions and other forces, are responsible for the formation of a stable complex.

Generally, one guest molecule is included in one cyclodextrin molecule, although in the case of some low molecular weight molecules, more than one guest molecule may fit into cavity, and in case of some high molecular weight molecules, more than one cyclodextrin molecule may bind to the guest. In principle, only a portion of the molecule must fit into the cavity to form a complex. As a result, one to one molar ratios are not always achieved, especially with high or low molecular weight guests.

Factors affecting complexation:

Following are some factors which affect complexation process,

1. Solution Dynamics.
2. Temperature.
3. Use of Solvents.
4. Water.
5. Volatile Guests (53).

Complexation Techniques:

Several techniques are used to form cyclodextrin complexes and include,

1. Physical mixture method:

Some drugs can be complexed by simply adding them to the cyclodextrin and mixing them together. It involves simple addition of guest molecule into CD and mixing them together.

2. Complexation as a paste (Kneading method):

An aqueous cyclodextrin paste is prepared by intensive mixing of cyclodextrin with a minimum amount of water in a kneading machine. Small quantities of paste are prepared using mortar and pestle. The guest compound (pure or dissolved in solvent e.g. ethanol) is added by Kneading to the paste of cyclodextrin for 3-4 hours. Additional quantity of water may be added during complexation procedure in order to keep paste Kneadable. The paste is then dried under vacuum at elevated temperature (e.g. 50⁰C) and resulting material is ground to obtain a powdery complex.

3. Complexation in organic solvents:

In special cases good complexation between CD-derivatives and hydrophobic guest compounds is observed in organic solvents. An equimolar mixture of cyclodextrin and the guest compound is dissolved in a polar, organic solvent (e.g. methanol). Sometimes CD and the guest molecules are dissolved in different solvents. To this 2-5% v/v water is added and the mixture is stirred for 6-8

hours at room temperature. After evaporation of the organic solvent the complex is dried under vacuum and ground to obtain a powdery material.

4. Co-precipitation method:

This is most widely used method in laboratory. In this method, CD is dissolved in water and the guest molecule is added to it while stirring the CD solution. More CD can be dissolved (20%) by heating the solution if the guest can tolerate the higher temperature. The CD and guest solution is cooled with stirring before the precipitate is formed. The precipitate is collected by decanting, centrifugation or filtration and washed.

5. Damp mixing:

The guest molecule and CD are thoroughly mixed and placed in a sealed container with a small amount of water. The contents are heated to about 100⁰C and then removed and dried.

6. Extrusion:

CD, guest molecule and water are premixed or are mixed when they are added to the extruder. The extruded complex is dried by placing in an oven provided the guest molecule is thermostable.

In all above methods, optimization of various variables such as the amount of water, degree and time of mixing, heating temperature heating time is necessary for each guest molecule separately.

Advantages of complexation with cyclodextrin:

Complexation with cyclodextrin offers various advantages and mainly include,

1. Alteration in the apparent solubility of the molecule
2. Improve patient compliance,
 - ✓ Reduce unpleasant odors
 - ✓ Taste masking

3. Protection of active ingredients against,

- ✓ Light, UV radiation
- ✓ Temperature
- ✓ Oxidation
- ✓ Hydrolysis

4. Prevent drug-drug, drug-additive interactions

5. Technology advantages,

- ✓ Stable, standardizable compositions
- ✓ More economical technological process (54).

Taste Masking by Ion-Exchange Resins (IER'S):

Ion Exchange Resins:

Ion exchange resins are high molecular weight, water insoluble polyelectrolytes that can exchange their mobile ion with the ions in the surrounding medium. Synthetic ion exchange resins have been used in pharmacy and medicine for taste masking and controlled release of drugs from as early as 1950s (38).

There are two major classes of ion-exchange polymers:

- Cation-exchangers – Whose functional groups can undergo reactions with the cations of the surrounding solution. There are two types of cation-exchangers;
 - Weakly acidic cation exchangers,
 - Strongly acidic cation exchangers.
- Anion-exchangers – Whose functional groups can undergo reactions with the anions of the surrounding solution. There are two types of anion exchangers;
 - Weakly basic anion exchangers,
 - Strongly basic anion exchangers (39).

Table 1: Trade names and manufacturers of some ion exchange resins (38)

Resin type	Chemical Constitution	Usual form as purchased	Trade names of equivalent ion-exchange resins			
Strongly acidic cation exchangers	Sulphonic acid groups attached to a styrene and divinylbenzene copolymer	$R-SO_3^-H^+$	Amberlite IR-120	Dowe x 50W	Duolite C-20	Lewatit S-100
Weakly acidic cation exchangers	Carboxylic acid groups attached to an acrylic and divinylbenzene copolymer	$R-COO^-Na^+$	Amberlite IRC-50	-	Duolite CC-3	Lewatit C
Strongly basic anion exchangers	Quaternary ammonium groups attached to a styrene and divinylbenzene copolymer	$[R-CH_2N-(CH_3)_3]^+Cl^-$	Amberlite IRA-400	Dowe x 1	Duolite A-101D	Lewatit M-500
Weakly basic anion exchangers	Polyalkylamine groups attached to a styrene and divinylbenzene copolymer	$[R-NH_2-(R)_2]^+Cl^-$	Amberlite IR-45	Dowe x3	Duolite A-7	Lewatit MP-60

Some Important Properties of Ion-Exchange Resins:

1. Cross-linkage:

The percentage of cross-linking affects the purely physical structure of the resin particles. The fraction of divinyl benzene in the resin determines the degree of cross linking and as to what extent the ion exchange resin is free to swell and shrink. The swelling in turn, affects the rate of hydration, the volume of expansion of resin in a column, the rate of ion exchange, and the capacity of the resin to absorb large molecules. This property is applied in the fact that Amberlite IRP-88 is used as a tablet disintegrant (37).

2. Porosity and Swelling:

Porosity is defined as the ratio of the volume of the material to its mass. The limiting size of the ions, which can penetrate into a resin matrix, depends strongly on the porosity. The porosity of an ion-exchanger depends not only on the amount of cross-linking substance used in polymerization but mainly on polymerization procedures. The structural parameters have a marked effect on the release characteristics of drug complexes.

3. Particle Size:

The rate of ion-exchange reactions depends on the size of the resin particles. Decreasing the size of resin particle significantly decreases the time required for the reaction to reach equilibrium with the surrounding medium. Most of the ion exchange resins are sold in the form of spherical beads. The most commonly used sizes of spherical beads are of 297-840 μm (20-50 mesh); they are best for column operations. Smaller size ranges (150-300 μm or 50-100 mesh; 75-150 μm or 100-200 mesh; 40-75 μm or 200-400 mesh) provide better chromatographic separations and may be more appropriate for pharmaceutical applications. A series of pharmaceutical-grade resins (AmberliteIRP from Rohm & Haas) have ranges of 40-150 μm (100-400 mesh).

4. Acid base strength:

The acid or base strength of an exchanger is dependent on the various ionogenic groups, incorporated into the resin. Resin containing sulfonic, phosphonic or carboxylic acid exchange groups have approximate pK_a values of <1, 2-3, and 4-6, respectively. Anionic-exchangers are quaternary, tertiary, or secondary ammonium groups having apparent pK_a values of >13, 7-9, or 5-9, respectively. The pK_a value of resin will have a significant influence on the rate at which the drug will be released from complex in the gastric fluids.

5. Stability:

The ion exchange resins are remarkably inert substances. At ordinary temperature and excluding the more potent oxidizing agents, vinyl benzene cross-linked resins are resistant to decomposition through chemical attack. Nevertheless, the materials are indestructible. Another

limitation of these resins is their degradation and degeneration in the presence of strong gamma ray sources (38).

6. Polymer Matrix:

The most commonly used polymer backbone for anion exchange and strong cation exchange resins are based on polystyrene. Divinylbenzene is included in the copolymerization for cross-linking the polymer chains. The weak cation exchange resins are generally polyacrylic or polymethacrylic acids.

7. Equilibrium Phenomena:

The principal property of these resins is their capacity to exchange bound or insoluble ions with those in solution. Soluble ions may be removed from solution through exchange with the counter ions absorbed on the resin as illustrated in the following equations;



These exchanges are equilibrium reactions in which the extent of exchange is governed by the relative affinity of the resin for particular ions. Relative affinity between ions may be expressed as a selectivity coefficient derived from the mass action expression as given below;

$$K_{DM} = \frac{[D]_r [M]_s}{[D]_s [M]_r}$$

where,

$[D]_r$ = drug concentration in resin

$[M]_s$ = its concentration in the solution

$[D]_s$ = the counter ion concentration in the solution

$[M]_r$ = concentration in resin

8. Exchange Capacity:

The capacity of an ion-exchanger is a quantitative measure of its ability to take up exchangeable counter-ions and is therefore of major importance. The exchange capacity refers to the number of ionic sites per unit weight or volume (meq. per gram or meq. per mL). The exchange capacity may limit the amount of drug that may be absorbed on a resin and hence the potency of the

complex. However, the preparation of drug complexes or resins, the actual capacity obtained under specific experimental conditions depends on the accessibility of the functional groups of the drug used for the study. Carboxylic acid resins derived from acrylic acid polymers have higher exchange capacities (about 10 meq/g) than sulfonic acid (about 4 meq/g) or amine resins because of bulkier ionic substituents and the polystyrene matrix. Therefore, higher drug percentages may often be achieved with carboxylic acid resins.

Properties of Drug: Resin Adsorbates:

Drugs adsorbed onto ion exchange resins have been referred to as adsorbates, complexes or resins. They are non-crystalline, usually spherical, hard, hydrate readily, have a totally insoluble, non absorbable cation or anion, and can be prepared in controllable particle-size ranges. Although they possess some properties similar to those of insoluble salts, the complexes differ from conventional salts which possess fixed ionic ratios. Differences in the resinate (complex), concentrations and properties can strongly influence the release or dissolution behavior of the drug. Although all ion-exchange resin adsorbates are designed for controlled dissolution, the differences in elution patterns allow for a number of specific applications (39).

Selection of Ion Exchange Resin:

Selecting the resin for a specific application requires consideration of a number of factors. Generally, the type charge (cation or anion exchanger) is obvious, although some amphoteric compounds may allow use of either type. For rapid dissolution in the GI tract, weak cation or anionic resins, low cross-linkage, small particle size, and high drug potency are required. Slow or gradual release or maximum taste protection may be obtained with strong cation or anion resins, high cross-linkage, a large size range, and lower drug content. If maximum potency or payload (mg drug per gram complex or resinate) is a requirement with a low-molecular-weight drug, a resin with a high exchange capacity (carboxylic acid resins) is chosen. A high molecular weight often limits the drug's ability to be absorbed, and very low cross-linkage may be necessary for meaningful loadings. Drug stability must be of concern when a sulfonic acid or quaternary amine may act as a catalyst for degradation even in the dry state. The hydrodynamics of the absorption process and economics are also of importance. In practice, the best approach is to select several

alternative resins, prepare adsorbates of different potencies, and rely on *in vitro* and *in vivo* testing for the best decision (38).

Preparation of Adsorbates:

The drug may be adsorbed on the ion-exchange resin by two methods;

1. Batch process,
2. Column process.

1. **Batch process:** This is the most preferred method for preparation of adsorbate because of its simplicity and quickness and the only alternative for very fine particles. A typical batch procedure involves slurring the resin in water, filtering or decanting the liquid on top, slurring the resin with the desired acid: base, or salt solution to change cycle (if necessary), decanting, and washing with water several times, and treating with the appropriate drug solution. After adsorption, the complex formed should be washed with water and dried.

2. **Column process:** A typical column procedure for preparing an adsorbate of an amine drug on a strong cation exchange resin, the resin is slurried in water. The slurry is added to a column and backwashed with water to eliminate air pockets and distribute the beads. Acid (e.g., HCl) is added to convert the acid cycle, followed by washing with water. Then a solution of drug is added, followed by washing with water. The cake is removed from the column, filtered by vacuum, and oven dried. An analogous procedure can be used to absorb a carboxylated drug on an anion exchange resin, using NaOH to convert the resin to the basic cycle. The washing of the resin with acid or the base is required to provide the essential exchangeable ions for the drug. This step is needed to be carried out for the resins which are non-pharmaceutical grade or doesn't come as pre-activated (39).

2. Pharmaceutical Applications of Ion Exchange Resins:

Ion-exchange resins have variety of pharmaceutical applications, stabilization of unstable drug, enhance the dissolution rate of poorly soluble drug, the complex of a deliquescent drug is not deliquescent, using resins or complexes completely eliminates any problems with polymorphism, change the physical state, tablet disintegrants, extended release dosage form ,

used in chewing gum for buccal absorption, bioadhesive systems for treatment of gastric mucosa, targeted drug delivery and cholesterol reducer (42).

Evaluation of taste masking

Sensory Analysis:

In developed countries, sensory analysis has been used for years to characterize flavors, odors, and fragrances. In current era to a great extent, evolution has been made in development of instrumentation method for characterizing odors and flavors. In aroma and flavor research, these methods are often more useful than in product development. In aroma and flavor research formulations are usually complex and sensory methods can provide equally reliable data on overall flavor character of a product.

Sensory analysis employs objective or analytical methods and subjective or hedonic methods.

A. Subjective Methods

1. Preference Testing

- a. Paired Testing
- b. Triangle Testing

2. Hedonic Scale

B. Objective Methods

1. Difference Test

- a. Paired Difference Test
- b. Triangle Difference Test
- c. Duo-Trio Test

2. Ranking Test

3. Analytical Test

- a. Flavor Profile
- b. Time-Intensity Test
- c. Single Attribute Test
- d. Dilution-Flavor Profiles

C. Statistical Tests (43).

CONCLUSION

Taste masking of bitter drug is common in pharmaceutical industries to develop a desired palatable and to enhance the onset of action. We have made an attempt to describe physiology and chemistry of taste, enlist various methods for taste masking of bitter drugs. Also highlighted on Complexation with Ion Exchange Resins and Formation of Inclusion Complexes with B-Cyclodextrin Derivative methods. Taste masking of the drug employing complexation and inclusion methods has proved to be safe and effective method for formulation of various dosage forms. Taste masking using complexation and inclusion become a potential tool to improve patient compliance, also both methods has broader application in various field.

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