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TASTE MASKING BY CO-CRYSTALLIZATION: A REVIEW

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ABSTRACT

Acceptability of any dosage form mainly depends on its taste i.e. mouth feel. Dosage form interacts with taste receptor on the tongue to give bitter, sweet or salty taste sensation, when it dissolves in saliva. In market, there are numbers of pharmaceutical preparations available in which actives are bitter in taste. Pediatric patients frequently fail to take medications properly because of unpleasant taste of medication. Thus bitterness of preparation leads to patient incompliance. So masking of bitterness becomes essential. To overcome this problem, many technique has been developed to mask the bitter taste of drugs. Co-crystallization involves alteration in molecular assemblies and composition of pharmaceutical substance and which ultimately results in enhancing physical properties. Co-crystals contains API and pharmaceutically acceptable co-formers. Co-crystals are molecular complexes, bringing about changes in solubility, bioavailability, stability and taste masking of bitter drug in pharmaceutical designing without interacting with therapeutic utility. The main objective of this review is discuss co-crystallization as a technique for masking the bitter taste of the drug.

KEYWORDS: Taste, Taste buds, Bitter drug, Taste masking, Co-crystallization, Sweetener.

INTRODUCTION

There are numerous pharmaceuticals that contain actives, which are bitter in taste. With respect to oral preparations, the bitterness of the preparation leads to lack of patient compliance. The problem of bitter and obnoxious taste of drug in pediatric formulations is a

challenge to the pharmacist in the present scenario. In order to ensure patient compliance, bitterness masking becomes essential.[1]

Oral Dosage Form

The oral route of administration is the most widely accepted route because of its convenience of self-administration, compactness and easy manufacturing.[2,3] But the most evident drawback of oral dosage form is the difficulty in swallowing and bitter taste, leading to patient incompliance in pediatric and geriatric patients.[2]

Organoleptic properties are an important consideration for development of a solid oral dosage form that can influence consumer preference and compliance. In the case of bitter drug, taste is one of the most important parameter governing patient compliance[4] and oral administration of bitter drug with an acceptable degree of palatability is a key issue for health care providers for pediatric and geriatric.[5]

The flavor of a substance is attributed to its taste, sight, odor and qualities such as mouth feel. Taste refers to a perception arising from the stimulation of taste buds present on the surface of the tongue. Taste masking becomes a pre-requisite for bitter drugs to improve the patient compliance especially in the pediatric and geriatric. To study various techniques of taste masking the basic information regarding taste sensation needs to be understood.[6]

Physiology of Taste

The sense of taste is mediated by taste bud, which are group of taste receptor cell (50 – 100 cells), bundled together in clusters like bananas and gives sensation of taste via sensory neurons to central nervous system (CNS) in the brainstem [Fig 1]. Taste buds are chemoreceptor stimulated by chemicals dissolved in saliva from oral ingested medicaments and enter via the taste pore followed by interaction with surface proteins known as taste receptors causing electrical changes with in taste cells, which cause the transmission of signals to the brain.[7]

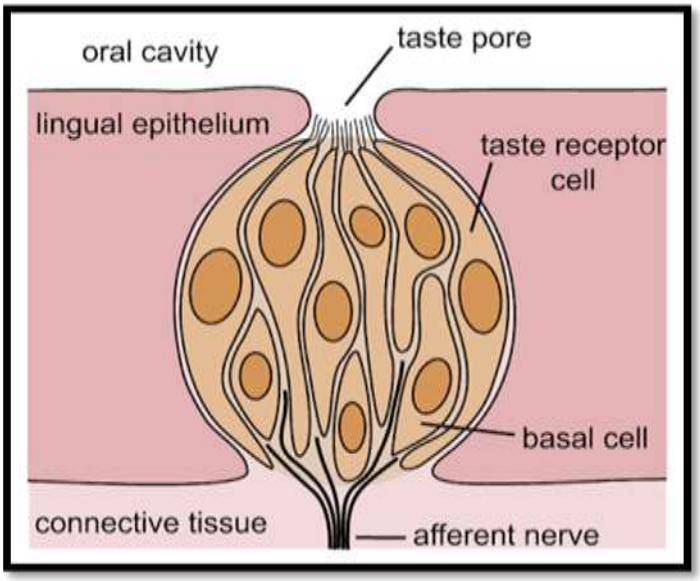

Fig. 1. Physiology of Taste buds

Four fundamental sensations of taste have been described[6, 8] - [Fig 2]

- Salty taste (edge, upper portion)
- Sweet taste (tip)
- Sour taste (along sides in back)
- Bitter taste (back)

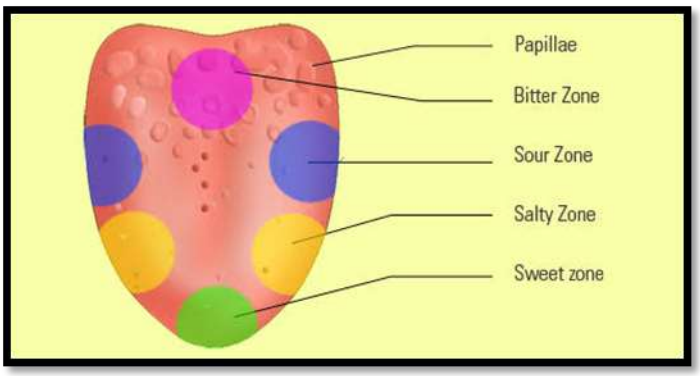

Fig. 2. Taste Points in Tongue

Table- 1: Compound Categorization for Taste Perception[9]

Taste Perception	Compounds
Sweet	Sugar, Saccharin, Alcohol
Sour	Acids (Dissociation of H in solution)
Salt	Metal ions (Inorganic salts)
Bitter	Donepezil, Ofloxacin, etc.

Mechanism of Action[10]

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 transduction 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.

Taste Signaling Pathways[11]

Taste transduction begins with the interaction of a tastant (e. g. medicine or food) with taste receptor cells in the taste buds (Fig 3). The tastant binds with G-Protein coupled receptors (GPCRS) in the cells triggering the release of G-Protein called Gustducin.

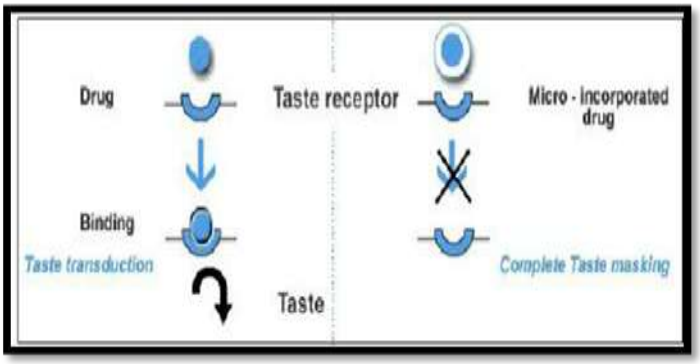

Fig. 3. Taste Signaling Pathway

The process of taste sensation begins when Gustducin activates the effector enzymes Phosphodiesterase IA (PDE) or phospholipase C beta-2 (PLC). The effector enzyme then changes the intracellular level of second messenger such as cyclic adenosine phosphate (cAMP), Inositol, 1, 4, 5- triphosphate (IP3) and diacylglycerol (DAG). The second messenger activates the ion channel including calcium channel inside the cell and sodium, potassium and calcium channel on extracellular membrane. This ionization depolarizes the cell causing the release of neurotransmitters that send nerve impulses to the brain that carries the signal of bitter taste and taste blockers work by interfering with taste transduction.[11] (Fig 4)

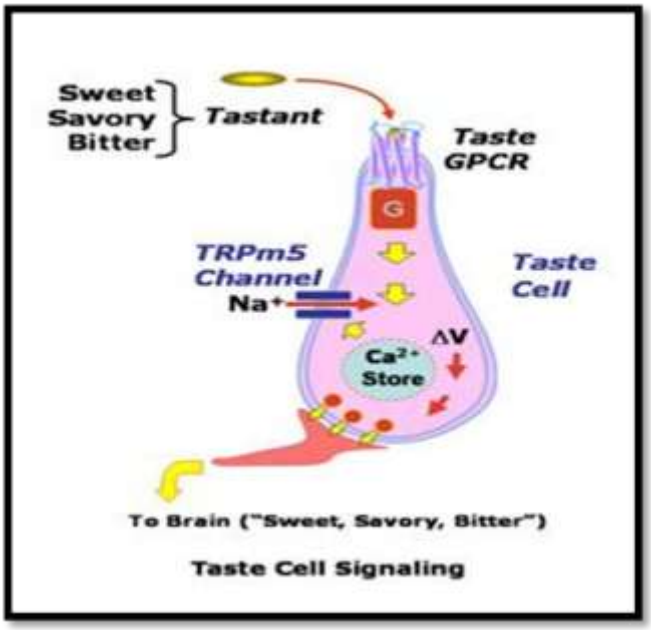

Fig. 4. Taste Blocking Mechanism

Effect of age on taste buds[12]

Cells that make up the taste buds with age are out, as a result taste buds begin to disappear from roof and the sides of the mouth except taste buds that are located over tongue. Remaining taste buds become less sensitive. Researches have been proved that smoking and eating of scalding food may damage to taste buds. This lacking of taste may lead to loss of appetite and poor nutrition. Taste is a type of medium to experience the world of taste for infants and young children. It is seen that children are more sensitive to certain taste than any adults because taste can be subjective the mechanism that causes taste sensitivity in youngsters can be difficult to analyze.

Causes of infected taste buds[12]

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 tissue in elderly and fungal infection (oral thrush) in those with decreased immunity.

Ideal Properties of Taste Masking Techniques[13]

It should

1) Require minimum number of excipients for an optimum formulation.

2) No adverse effect on drug bioavailability.

3) Require excipients that are economical and easily available.

4) Least manufacturing cost.

5) Can be carried out at room temperature

6) Require excipients that have high margin of safety.

7) Involve least number of equipment processing steps.

8) Rapid and easy to prepare.

Factors affecting selection of taste masking technology[14]

1) Extent of the bitter taste of the API.

2) Required dose load.

3) Drug particulate shape and size distribution.

4) Drug solubility and ionic characteristics.

5) Required disintegration and dissolution rate of the finished product.

6) Desired bioavailability.

7) Desired drug release profile.

8) Required dosage form.

Approaches of taste masking[11]

1) Reduction of drug solubility in saliva.

2) Create a barrier between taste receptor and drug.

3) By adding flavors or sweeteners.

TASTE MASKING METHODS

1. Addition of flavoring and sweetening agents

It's the common method for taste masking. But its use is limited to highly bitter actives. Different grades of sweeteners are available in order to control the taste. The following table 2 gives a compilation of most common artificial and natural sweeteners with their relative sweetness to sucrose and comments pertaining to each.

Table-2: Relative sweetness of commonly used sweeteners[15]

Sweeting agent	Relative sweetness	Comment
Aspartame	200	Not very stable in solution
Acesulfame potassium	137-200	Bitter after taste if used in higher concentration
Cyclomate	40	Banned
Glycyrrhizin	50	Moderately expensive
Lactose	0.16	Large amount required

Mannitol	0.60	Negative heat of solution
Saccharin	450	Unpleasant after taste
Sucrose	1	Most commonly used
Sucralose	600	Synergistic sweetening effect

Flavor is a complex effect of three components taste, odor and feeling factors.[16] Suitable flavors are selected through taste panel studies. Most of the times, a blend of flavors is used for masking the taste. Now since many flavors are odorous, the brain receives some additional impulses from the olfactory receptors in the nose which coordinate with the gustatory stimuli to produce the mingled sensation that is recognized as the flavor of a substance.[17]

Table-3: Flavoring agent used to mask basic taste

Basic taste	Flavoring agent
Sweet	Vanilla, Bubble Gum, Grapefruit
Acid	Lemon, Lime, Orange, Cherry, Grape fruit
Metallic	Grape, Marrsh, Mellow, Gurana, Berries, Mints
Bitter	Liquorice, Coffee, Chocolate, Mint, Grapefruit, Cherry, Peach, Raspberry, Orange, Lemon, Lime

2. Ion-exchange resin complex[18]

Ion exchange resins are synthetic organic polymers inert in nature, consists of a hydrocarbon chain to which insoluble groups are attached and they have ability to exchange their labile ions for ions present in the solution with which they are in contact.

Types-

- **Cation exchange resins-** exchanger of sodium, potassium or aluminum salt.
- **Anion exchange resins-** exchanger of chloride salt.

Drug loaded on to the resins by two methods-

- Column method
- Batch method

3. Microencapsulation[19]

Microencapsulation is a process in which the active moiety (solid or liquid droplet) is coated with a polymeric material or film.

Types of microencapsulation include-

- Air suspension coating
- Coacervation phase separation
- Spray drying
- Spray congealing
- Solvent evaporation
- Pan coating

4. Prodrug approach[20]

A prodrug is chemically modified inert drug precursor which upon biotransformation liberates the pharmaceutically active parent compound.

Two approaches are use to overcome these problem-

a. Reduction of drug solubility in Saliva.

b. To lower the affinity of drug to taste receptors.

5. Inclusion complexation[21]

In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent i.e., the host molecule forming a stable complex. The complexing agent is capable of masking the bitter taste of the drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds thereby reducing the perception of bitter taste. Vander Waals forces are mainly involved in inclusion complexes. Cyclodextrin is the most widely used complexing agent for inclusion complex formation.

6. Granulation[22]

In this method, saliva insoluble polymers are used as binding agents. As these polymers are insoluble in saliva, thus the bitter taste of the drug can be masked. Granulation lowers the effective surface area of the bitter substance that come in contact with the tongue upon oral intake.

7. Multiple emulsion technique[23]

A novel technique for taste masking of drugs employing multiple emulsion 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.

8. Gel formation[24]

Water insoluble gelation on the surface of tablet containing bitter drug can be used for taste masking. Sodium alginate has the ability to cause water insoluble gelation in presence of Bivalent metal ions.

CO-CRYSTALLIZATION

This is a novel approach for masking the taste of bitter drug. The successful delivery of any active pharmaceutical ingredient (API) to patients requires the ability to manufacture effective drug products. Common problems that challenge the successful drug delivery and manufacture include deficiencies in their properties, such as solubility, stability, bioavailability, organoleptic properties and mechanical properties. Co-crystallization is one of the emerging crystal engineering techniques for modulating pharmaceutical performance through controlling solid- state properties of APIs. This is possible because co-crystallization significantly expands the access to new solid forms differing in structures.[25] Generally it involves the slow evaporation of solutions with equimolar or stoichiometric concentrations of the components. In this process, there's always the risk of crystallizing only the single components.[26]

Co-crystal

Co-crystal is lattice arrangement composed of two or more components in stoichiometric compounds. Co-crystal can be composed of either atomic, molecular or ionic compound. Co-crystallization is a development method for pharmaceutical raw material in order to get the desired physicochemical properties, such as solubility, physical stability, bioavailability, flowability and compressibility of an active compound without altering its biological activity.[27] In recent years, co-crystal formation has emerged as a viable strategy for improving the solubility and bioavailability of poorly soluble drugs. They can be constructed through several types of interactions, mainly non-covalent ones, such as hydrogen bonding, π-stacking, and van der Waals forces. A pharmaceutical co-crystal contains an API and a co-former molecule(s) that form a unique crystalline structure having unique properties and interact by hydrogen bonding or by other non-covalent bonds.[28]

Crystal engineering and Design of Co-crystals

Co-crystal design is based on crystal engineering principles. The term ‘crystal engineering’ refers to engineering or construction of crystalline solids with desirable properties and is based on a fundamental understanding of inter-molecular interactions that govern the

assembly of molecules into a network superstructure.[29,30] The molecules in the network are held together by synthons that are basic structural units formed from non-covalent interactions such as van der Waals interactions, $\pi - \pi$ interactions and hydrogen bonds between the functional groups in the molecules.[31,32]

Physicochemical properties of Co-crystals

Physical and chemical properties of co-crystals are of great importance to the development of APIs. The overall motivation for investigating pharmaceutical co-crystals as an alternative approach during drug development is the adjustment of the physiochemical properties to improve the overall stability and efficacy of a dosage form.[33] Physicochemical properties, such as crystallinity, melting point, solubility, dissolution and stability, have been studied extensively by researchers.

- **Melting Point**

Melting point is the temperature at which the solid phase is at equilibrium with the liquid phase. It is a fundamental physical property and an important consideration during solid drug development. There are complex correlations between the melting point of pharmaceutical product and its processability, solubility and stability. Much research work has been carried out to investigate if the melting point of a co-crystal changes with respect to the individual components and if the melting points can be estimated and modulated within a series of co-crystals.[34]

- **Stability**

Stability is a very important parameter when evaluating the properties of a pharmaceutical co-crystal. Usually, the stability testing of a newly developed co-crystal includes four aspects: relative humidity stress, thermal stress, chemical stability and solution stability. The relative humidity stress test is used to identify the best storage conditions for the product because the amount of water present in the co-crystal can lead to quality deterioration. Thermal stress and chemical stability are relatively less studied areas about co-crystal properties. Very few reports were found and these limited studies showed that thermal stress studies can Provide valuable information about physicochemical stability. Meanwhile, assessing chemical stability of co-crystals is important when developing of these materials.[34]

- **Solubility**

Co-crystal solubility is dependent on co-crystal component oncentration, solution complexation and ionization when one or more components are ionizable.[35] Traditional methods for improving solubility of poorly water-soluble drugs include salt formation, solid dispersion (emulsification) and particle size reduction (micronisation).[36]

- **Intrinsic Dissolution**

Intrinsic dissolution measures the rate of dissolution of a pure drug substance from a constant surface area, which is independent of formulation effects and measures the intrinsic properties of the drug as a function of dissolution media, e.g. pH, ionic strength and counter-ions. The sample used in the intrinsic dissolution test is pressed into a disk or pellet, which should be no form change upon pressing and the disk, needs to remain intact during the experiment.[37]

- **Bioavailability**

Bioavailability is a measurement of rate and extent of API that reaches to the systemic circulation. The bioavailability of newly formed moiety is determined with the help of animal experimentation. The ultimate goal for co-crystal investigation is to improve bioavailability of an APIs. Animal bioavailability is an important for a newly prepared compound. There are limited numbers of animal bioavailability studies on co-crystals.[34]

Advantages of Co-crystals[35, 38]

1. Co-crystal can enhance the solubility.
2. It can be utilized for non- ionisable API.
3. Strong inorganic acid co-crystals sulfonates, sulfates, hydrochlorides, etc., increase melting point and enhance the crystallinity, which can lead to increased stability including thermal.
4. In chemical processing co- crystal formation may be used as a purification step.
5. It helps in improving bitter taste of drugs.
6. Applicable for wide range of drugs.
7. It is simple technique.
8. Lower cost involved.
9. Reduce chemical degradation when expose to light.

Disadvantage of co-crystals[39]

1. Selection of the suitable solvent is tedious process.

2. Maintenance of processing parameters (temperature, agitation) is difficult.

3. For parenteral and product line extension products, there is a risk of in-situ formation of a less soluble form.

4. Co-crystal of weak carboxylic acids tend to have lower melting points, which can result in higher levels of amorphous API.[40, 41]

Application of Co-crystals[42]

Compared to other solid-state modification techniques, co-crystal formation appears to be an advantageous alternative for drug discovery (e.g. new molecule synthesis, nutraceutical co-crystals), drug delivery (solubility, bioavailability) and chiral resolution.

Co-formers used in Taste masking

Table-4: Co-former with sweetness index

Co-former	Relative Sweetness
Sucrose	1
Glucose	0.75
Dextrose	0.75
Mannitol	0.5
Sucralose	600
Saccharin	300
Aspartame	180
Neotame	1200/1300

Different methods of Co-crystallization[43, 44]

1. Solvent Evaporation

Solvent evaporation is the most conventional method in case of crystallization. In this technique the all material is mixed with the common solvent serially and evaporated completely. During evaporation stage the solution of molecules are expected to undergo various hydrogen bonding reactions. But in case of co-crystallization which consists of co-former and active ingredient, solubility of both in the selected solvent plays a great role. If the solubility of both is not similar, then the one with low solubility than the other will precipitate out. Molecule has ability to participate in the intermolecular interaction to form a co-crystal. The major disadvantage of this method is that it requires large amount of solvent.[45]

2. Grinding[46]

Solid state grinding is where the materials are mixed, pressed and crushed in a mortar and pestle.

a. Slurring

Slurry crystallization is simple process which includes the addition of crystallization solvent in the API along with its acceptable former.

b. Solvent drop grinding-

Modification of solid grinding technique is this technique where two materials can be grinded by adding a minor quantity of solvent. The criteria of this technique being the solvent added is in very minute quantity which when added acts as a catalyst but does not form a part of the end product.

3. Anti-solvent method[46]

This is one of the methods for precipitation or recrystallization of the co-crystal former and active pharmaceutical ingredient. Solvents include buffers (pH) and organic solvents.

4. Sonocrystallization[47]

The development of sonochemical method for preparation of organic co-crystals of very finite size has been done. This method was primarily developed for preparation of nanocrystals. Caffeine-maleic acid co-crystal preparation commenced with use of ultrasound method.

5. Cooling crystallization[48]

Dissolving your solute in a solvent system to give a near saturated solution at one temperature and then letting the system cool to a lower temperature.

6. Hot melt extrusion[49]

Extrusion is useful method for synthesis of co-crystals, it involves highly efficient mixing and improved surface contacts, Co crystals are prepared without use of solvent. The selection of this method is primarily depends on thermodynamic stability of compound.

EVALUATION OF TASTE MASKED FORMULATION

- **Sensory evaluation**

To quantitatively evaluate taste sensation, following methods have been reported in literature.

a. Panel testing (human subjects)[50]

In this method, a group of about 5-10 human volunteers is trained for taste evaluation by using reference solutions ranging in taste from tasteless to very bitter. Numerical values are then assigned to these levels of bitterness (e.g. 0-5).

b. Measurement of Frog Taste Nerve Responses[51]

In this method, adult bull frogs are anaesthetized intraperitoneal and the glossopharyngeal nerve is then located and dissected from the surrounding tissue and cut proximally. An ac-amplifier and an electronic integrate the nerve impulses. The peak height of the integrated response is then taken as the magnitude of response.

c. Electronic (E) tongue[52]

This is an automated taste sensing device to detect the magnitude of bitterness of drug substance. The device has a transducer which is composed of several kinds of lipid/ polymer membranes with different characteristics that can detect taste in manner similar to human gustatory sensation. Taste response is transferred into a pattern composed of electric signals of membrane potentials of the receptor part. Different response electric potential pattern are obtained for substances producing different taste qualities.

d. Spectrophotometric method[53]

A known quantity of the taste masked formulation is mixed with 10ml of distilled water in 10ml syringe by revolving the syringe, end to end; 5 times in 30 seconds. The 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.

CONCLUSION

Taste masking is a viable strategy to improve the patient compliance, especially for bitter drugs. Taste masked products developed from innovative pharmaceutical technologies not only increase the commercial profits, but also create brand value for a company. Improvement of bitter taste drug using sweeteners as conformer by co-crystallization. It not only improve the taste of drug but also improve their physicochemical properties such as solubility, stability, dissolution and bioavailability of drug.

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