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Review Article

Advance Approaches in Taste Masking for Pharmaceutical Formulation

Ashish Jagtap, Gajanan Vaishnav, Suwarna Kale, Suyog Joshi, Ashwini Khairnar
Yash Institute of Pharmacy, Aurangabad, Maharashtra, India- 431134

ABSTRACT

Oral administration of pharmaceutical is one of the most popular methods of drug delivery. Acceptability of any dosage form are mainly depends over its taste i.e. Mouth feel drug molecules interacts with taste receptor on the tongue to give bitter, sweet or salty taste sensation. When they dissolve in saliva .This sensation of the taste is result of signal transduction from the receptor organ for taste commonly known as taste buds and Palatability is an extremely important factor in ensuring the likelihood that the recipients will intake the pharmaceuticals. A constant problem is in treatment of patient is their inability or unwillingness to swallow solid dosage forming such as tablets especially in children and the elderly. .In market, there are number of pharmaceutical preparation available in which actives are bitter in taste. The improved palatability in these products has prompted the development of numerous formulations, which improves performance and acceptability. So masking of bitterness becomes essential. Previously the attitude of "Worse the taste of medicine, the better the cure" was observed, but now-a-days several approaches of masking the bitter taste have been developed. It include adding sugars, flavours, sweetness, use of lipoproteins, numbing taste buds, granulations ,adsorptions, microencapsulation, multiple emulsion, prodrug and salts formulation, inoculation and molecular complexes, solid dispersion, application of Ion Exchange Resins(IERs). This article reviews the methodologies and approaches of taste masking taste masking techniques of bitterness reduction and also reviews the various evaluation techniques such as Panel testing (human subjects), Measurement of frog taste nerve responses, Multichannel taste sensor/ magic tongue, Spectrophotometric evaluation/ D30's value method.

Keywords: Taste masking, evaluation,

Address for Correspondence:
Ashish Ashok Jagtap
Yash Institute of Pharmacy, South City, Bajaj Nagar, Aurangabad (M.S.) India-431134
Email id: ashishjagtap987@gmail.com
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INTRODUCTION

Acceptability of any dosage form are mainly depends over its taste i.e. mouth feel taste is an important parameter in case of drugs administering orally. Psychologically human can detects four kinds of taste, sweetness, saltiness sour and bitterness. Several pharmaceutical drugs have unpleasant taste most of them being bitter. The major consequences of unpleasant taste are insufficient compliance from the patients and especially from infant, children's and elderly. The bitter taste modality is an undesirable trait of the products or formulations and can considerably affects its acceptability by consumers. There are numerous pharmaceutical and OTC (Over the counter)preparations that contains actives , which are bitter in taste with respect to OTC preparation, such as cough and cold syrups the bitterness of the preparation leads to lack of patients compliance. Children are frequently failed to take medications properly because of unpleasant taste of medicament. Non-compliance can lead to worsening of diseased condition. An ideal taste masking process should effectively mask the taste with the minimum use of expedients should be easily available and economical and be effective.

Two approaches are commonly used or utilized to overcome bad taste of the drugs. [1]

- First approach is to reduction of drug solubility in saliva where a balance between reduced solubility and bioavailability must be achieved.
- Second approach is to alter the ability of the drug to interact with taste receptors.

To overcome this problem several techniques are evolved to mask the bitter taste of drugs. These techniques not only serve to mask the taste of a drug but also enhance the

Bioavailability of drug dosage forms. Commonly used techniques that are adopted for large scale production of pharmaceutical dosage forms are use of flavors and sweetener, coating of drug particles with inert materials, formation of inclusion complexes, ion exchange resin approach, spray drying, microencapsulation, liposomes, prodrugs, adsorption, multiple emulsions and formation of molecular complexes of drug with other chemicals are reported. So, any pharmaceutical formulation with a pleasing taste would definitely be preferred over a competitor's product and would translate into better compliance and therapeutic value for the patient and more business and profits for the company. The desire of improved palatability in these products has prompted the development of numerous formulations with improved performance and acceptability.

The taste masking is also having some advantages such as:-[2]

- Taste masking of bitter drug improve the patients compliance.
- It also improves stability of some drugs.
- It improves the therapeutic efficacy and bioavailability of certain drugs.
- It improves organoleptic characteristics of drugs.

The need for taste masking

Many drugs actives are intensely bitter or have other aversive taste, aroma, texture or mouth feel attributes are frequently unknown or inadequately addressed during development resulting in drug products that may not be tolerated by patients.

When drug products are not properly taste masked. Dosing compliance and health outcome suffer. This is especially true for paediatrics formulations or drugs for adults who have difficulty swallowing.

The need to formulate taste masked oral formulation [3]

Children, older persons-

- Trouble in swallowing tablets or capsules.
- Prefer liquid or sublingual/chewable solid dosage form

Undesirable taste-

- Important formulations problems in case of oral formulation
- Patients compliance

To study various technique of taste masking the basic information regarding taste sensation need to be understood

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 thebrainstem4. Taste buds are chemoreceptor stimulated by chemicals dissolved in saliva from oral ingested medicament sand enter via the taste pore followed by Interaction with surface proteins known as taste receptors causing electrical changes within taste cells, which cause the transmission signals to the brain. [4]

Four fundamental sensations of taste have been generally described- Sweet, Sour, Bitter, Salty and fifth widely accepted basic taste is Umami.

Salty taste (edge, upper portion)

The salty is one among the four taste receptors of tongue. They are located on the edge of upper front portion of the tongue

Sweet taste (tip)

The sweet taste is one among the four taste receptors in the tongue .they are found on the tip of the tongue

Sour taste (Alongside in back)

The sour taste is also one of the four taste receptors of the tongue. They occurs at side of the tongue and are stimulated mainly by acids

Bitter taste (back)

The bitter taste is the last and one of the four taste receptors in the tongue that is located towards the back of the tongue. It is stimulated by a variety of chemicals substance, most of which are organic compounds, although some inorganic compounds such as magnesium and calcium also produce bitter sensations.[5]

Umami taste

Umami is the taste of certain amino acids (e.g. glutamate, aspartate and related compounds). It was first identified by Kikunae Ikeda at the Imperial University of Tokyo in 1909. It was originally shown that the metabotropic glutamate receptor (mGluR4) mediated umami taste. Binding to the receptor activates a G-protein and this elevates intracellular Ca2+. More recently it has been found that the T1R1 + T1R3 receptors mediate umami taste. Humans receive tastes through sensory organs, taste buds (also known

as gustatory calculi) concentrated on the upper surface of the tongue. [6]

Different types of tastes have different threshold concentration based on the distribution of taste buds on surface of the tongue, enlisted in Table 1.

Taste	Area of Tongue	Threshold concentration (%)
Sweet	Tip of tongue	0.5
Salt	Tip and side of tongue	0.25
Sour	Side of tongue	0.007
Bitter	Back of tongue	0.00005

Table 1: Specific area of tongue and threshold concentration for primary taste sensations

Taste Signaling Pathways

Taste transduction begins with the interaction of a tastant (e.g. medicine or food) with taste receptor cells in the taste buds8 (Fig 3). The tastant binds with Protein coupled receptors (GPCRS) in the cells triggering the release the release of G-Protein called Gustducin

The process of taste sensation begins when Gustducin activates the effecter enzymes phosphodiesteraseIA (PDE) or phospholipase C beta-2(PLC).The effecter enzyme then changes the intracellular level of second messenger such as cyclic adenosine monophosphate (cAMP), Inositol, 1, 4, 5- triphosphate (IP3) and diacylglycerol (DAG). The second messengers activate 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 ta transduction9. [4]

Ideal properties for taste masking process [7]

1 It should, be physically and chemically inert in nature

2 Involves least no. Of equipments and processing steps

3 Excipients should be economical and easily available

4 It shows high margin of safety

5 Least manufacturing cost

6 Rapid and easy to prepare

- 7 Be stable at room temperature

Factors that are taken into consideration during the taste-masking formulation process include: [8]

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 release profile.

8) Required dosage form.

Taste masking techniques:

Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist. Methods commonly used for taste masking involves various physical and chemical method that prevent the interaction of taste bud with drugs, Two approaches are commonly utilized to overcome bad taste of the drug

.1. By reducing the solubility of drug in the pH of saliva (5.6 - 6.8).

2. By altering the affinity and nature of drug which will interact with the taste receptor.[9]

1. Taste masking with sweeteners and flavours

Flavours and sweeteners

This technique is simplest approach for taste masking. But this approach is not very successful for highly bitter drugs. Artificial sweeteners and flavors are generally being used along with other taste-masking techniques to improve the efficiency of these techniques [10]. Eucalyptus oil is a major constituent of many mouth washes and cough drop formulations which is a bitter tasting substance. Its bitter taste can be masked by agent including fenchone, borneol or isoborneol [11].

Cooling effect of certain flavoring agent aids in reducing perception of bitterness. The physiology involved is merely to numb taste buds, either rapidly or over a period of time, so that the cooling effect actually builds up after ingestion. The brain perceives the coolness even though physically the temperature of the product has not changed [12]. Some generalization concerning the selection of flavors to mask specific types of taste has been suggested. [13]

A combination of flavoring agents is usually employed. Flavor adjuvant like menthol and chloroform are considered as a desensitizing agents because addition to their own odour and flavor they also have mild anesthetic effect on taste receptors. Aspirin medicated floss contains sodium phenolate as an anaesthetizing agent in addition to chocolate flavor to mask the bitter taste of aspirin. A survey of the taste preferences of human race, as a whole, indicates that sweet taste is very agreeable to our species. Hence for controlling the taste qualities effort are directed to make the preparations sweet to different

degrees. A survey of the taste preferences of human race, as a whole, indicates that sweet taste is very agreeable to our species. Hence for controlling the taste qualities effort are directed to make the preparations sweet to different degrees. Sweeteners are commonly used for this purpose. Table 2 presents a compilation of the most common artificial and natural sweeteners used in pharmaceutical products, their relative sweetness levels, and pertinent comments. Aspartame is used as prominent sweetener in providing bitterness reduction. A very small concentration (0.8%) is effective in reducing bitterness of 25% acetaminophen. Cyclamates have been banned by the USFDA since 1970 due to its carcinogenic effect. The neohesperidinedihydrochalone is an artificial bitterness suppressor and flavor modifier. It is an open chain analogue of neohesperidine, a bitter flavanone that occurs in Seville oranges (citrus aurantium). Taste masking properties of the neohesperidinedihydrochalone have been reviewed by Cano et al. It is a bitterness suppressor and flavor modifier that also elicits a very intense lingering sweet taste. Due to its lingering sweet taste the taste of bitter substance appears later in time and taste could be masked.

Active ingredient is significantly objectionable in taste then flavors alone are unable to yield a completely satisfactory product. Major taste masking efforts are required before they are acceptable for market trials. But this approach can always play a significant supportive role to other taste masking approach.

Sweetening Agents	Relative sweeteners*	Significance
Aspartame	200	Less stable in solution
Acesulfame potassium	137-200	Bitter in higher concentration
Cyclamate	40	Banned
Glycerrhizin	50	Moderately expensive
Lactose	0.16	High amount is required
Manitol	0.60	Negative heat of solution
Saccharin	450	Unpleasant after taste
Sucrose	1	Most commonly used
Sucralose	600	Synergestic sweetening effect

Table 2: List of commonly used sweeteners and their relative sweetness [14]

Type	Example	Comments
Natural	Peppermint	Less stable
Artificial	Vanilla	Highly stable
Natural and artificial	Strawberry	Effective at low concentration

Table 3: Classification of flavoring agents[13]

2. Polymer coating of drug

This is the simplest and most feasible option to achieve taste masking. The coating acts as a physical barrier to the drug particles, thereby minimizing interaction between the drug and taste buds. Coating of chewable tablets provides excellent taste masking while still providing acceptable bioavailability. In this approach, powders as fine as 50 mm are fluidized in an expansion chamber by means of heated, high-velocity air, and the drug particles are coated with a coating solution introduced usually from the top as a spray through a nozzle. [15] Any nontoxic polymer that is insoluble at pH 7.4 and soluble at acidic pH, would be an acceptable alternative for taste masking. Taste masking of ibuprofen has been successfully achieved by using the air suspension coating technique to form microcapsules, which comprises a pharmaceutical core of a crystalline ibuprofen and methacrylic acid copolymer coating that provides chewable taste masked characteristics.

Agents used for coating

- Carbohydrates (Cellulose)
- Synthetic polymers (Eudragitsetc)
- Proteins, Gelatine, and Prolamines (Zein)
- Zeolites[14]

It is classified based on the type of coating material, coating solvent system, and the number of coating layers. Hydrophobic polymers, lipids, sweeteners and hydrophilic polymers can be used as coating materials, either alone or in combination.[15,16]Multilayer coating has been used to overcome the challenges of coating imperfections, which otherwise lead to a decline in the taste masking performance, especially for the aggressively bitter drugs. The core materials were coated with a first smooth and uniform spacing layer, which can minimize the coating imperfections during the second layer coating and can also act as an instant barrier between the taste receptors and the bitter core material.

3. Taste masking by Microencapsulation:[16]

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. Coating is an extremely useful technique for a number of applications in pharmaceutical field. Although it is used

primarily for production of sustained release, Gastro-intestinal dosage forms, it also has major applications in masking the unpleasant taste. It is important to understand that only soluble portion of the drug can generate the sensation of taste. Coating the active drug with a properly selected polymer film can reduce its solubility in saliva and thus taste could be masked. Coating the drug particles created a physical barrier between the drug and the taste buds and taste of active could be masked.

The goal of Microencapsulation may be accomplished by any of the following techniques.

1.Air suspension coating
2.Coacervation - phase separation
3.Spray drying and spray congealing
4.Solvent evaporation
5.Multiorifice - centrifugal process
6.Pan Coating
7.Interfacial polymerization

1. Air suspension coating

The air suspension coating process can appropriately be described as an upward moving, expanded, fluidized bed in central portion of the coating chamber coupled with a downward moving, more condensed fluidized bed on the periphery of the column. Three types of air suspension coaters are available, namely, top spray coater, wurster bottom spray coater and tangential spray coater.

2. Coacervation- phase separation

Coacervation-phase separation involves following three steps.

A) Formation of three immiscible chemical phases- The first step of coacervation phase separation involves the formation of three immiscible chemical phases: a liquid vehicle phase, a coating material phase and a core material phase. The three phases are formed by dispersing the core material in a solution of coating polymer, the vehicle phase is used as a solvent for polymer. The coating material phase consists of a polymer in a liquid phase, is formed by using one of the of phase separation-coacervation method, that is by changing the temperature of the polymer solution, by adding a solution, or by inducing a polymer- polymer interaction.

B) Core material phase –The process consists of depositing the liquid polymer coating upon the core material. This is accomplished by controlled, physical mixing of the coating material and the core material in the manufacturing vehicle. Deposition of the liquid polymer coating around the core material occurs if the polymer is absorbed at the interface formed between the core material and the liquid vehicle phase, and this adsorption phenomenon is a prerequisite to the effective coating.

C) Coating material phase- The process involves the rigidizing the coating, usually by thermal, cross-linking or desolvation techniques, to form self-sustaining microcapsule.

Advantages of spray drying technique [17]

- Simple and rapid process
- Control of particle size, shape, porosity and density
- Reproducible and scalable
- Require mild temperature conditions
- Produces free flowing and spherical particles
- Requires no additional processing before compaction into tablets
- Enhanced dissolution rate of drugs
- Cost effective

3. Spray drying and spray congealing

Spray drying and spray congealing processes are similar in that both involve dispersing the core material in a liquefied coating substance and spraying or introducing the core coating mixture into some environmental condition, whereby, relatively rapid solidification (and formation) of the coating is affected. The principal difference between the two methods is the means by which coating solidification is accomplished. Coating solidification in the case of spray drying is effected by rapid evaporation of a solvent in which the coating material is dissolved. Coating solidification in spray congealing methods, however, is accomplished by thermally congealing a molten coating material or by solidifying a dissolved coating by introducing the coating - core material mixture into a non-solvent. Removal of the solvent or solvent from the coated product is then accomplished by sorption, extraction, or evaporation techniques.

4. Solvent evaporation

The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dissolved in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core coating material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated (if necessary) to evaporate the solvent for the polymer. In the case in which the core material is dispersed in the polymer solution, polymer shrinks around the core. In the case in which core material is dissolved in the

coating polymer solution, a matrix - type microcapsule is formed. Once all the solvent for the polymer is evaporated, the liquid vehicle temperature is reduced to ambient temperature (if required) with continued agitation. At this stage, the microcapsules can be used in suspension form, coated on to substrates or isolated as powders.

5. Multiorifice- Centrifugal process

Processing variables include the rotational speed of the cylinder, the flow rate of the core and coating materials, the concentration and viscosity of the coating material, and the viscosity and surface tension of the core material. The Multiorifice- centrifugal process is capable of microencapsulating liquids and solids of varied size ranges, with diverse coating materials.

6. *Pan coating*

The pan coating process, widely used in the pharmaceutical industry, is among the oldest industrial procedures for forming small, coated particles or tablets. The particles are tumbled in a pan or other device while the coating material is applied slowly. The problem of bitter and obnoxious taste of drug in paediatric and geriatric formulations is a challenge to the pharmacist. 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.

7. Interfacial polymerization

The methods involve the reaction of monomeric units located at the interface existing between a core material substance and a continuous phase in which the core material is dispersed. The continuous or core material supporting phase is usually a liquid or gas, and the polymerization reaction occurs at a liquid-liquid, liquid-gas, solid-liquid, or solid-gas interface [5].

Polymers used for coating in Microencapsulation [8]

Coating is an extremely useful technique for number of applications in the pharmaceutical field. It is classified based on the type of coating material, coating solvent system, and the number of coating layers. By coordinating the right type of coating material it is possible to completely mask the taste of a bitter drug, while at the same time, not adversely affecting the intended drug release profile. Polymers have been exclusively used as coating materials, either alone or in combination, as a single or multi-layer coat, in the taste masking of bitter medicaments. Combinations of pH independent water insoluble polymers such as cellulose ethers, cellulose ester, polyvinyl acetate and water soluble polymers such as cellulose acetate butyrate, polyvinyl pyrollidone, hydroxyethyl cellulose have been used to attain a balance between the taste masking and in vitro release.

Hydrophobic polymers have been popularly used for coating bitter medicaments to achieve taste masking. These coating agents simply provide a physical barrier over the drug particles. However, hydrophilic polymers may also providetaste masking of Ibuprofen, by coating with hydrophilic polymers such as hydroxyethyl cellulose or a mixture of hydroxyethyl cellulose and hydroxypropyl methylcellulose. Sweeteners can be included in the coating solution for a better taste masking performance. One of the most efficient methods of drug particle coating is the fluidized bed processor. In this approach powder as fine as 50ìm, are fluidized in expansion chamber by means of heated, high velocity air and the drug particles are coated with a coating solution introduced usually from the top as spray through nozzle. The coated granules are dried with warm air.

Some advantages of taste masking by microencapsulation [17]

- Taste masking can be achieved with the desirable fast or controlled drug release
- Coating may increase the stability of the dose and dosage form
- Bitter liquids may be achieved with the desirable fast or controlled drug release
- The coated bitter particles can adapt to a wide variety of dosage form and product applications.

4. Taste masking by ion exchange resins:(IER)- [18]

One of the popular approaches for taste of bitter drugs is based on ion exchange resins. Ion exchange resins are synthetic organic polymers inert in nature, consist of a hydrocarbon chain to which insoluble groups are attached and they have ability to exchange their labile ions for ions present in solution with which they are in contact. IER are solid high molecular weight poly electrolytes that can exchange their ions of equal charge with surrounding medium. These groups have affinity for oppositely charged counter ions. IERs contain positively or negatively charged sites and are classified as cation or anion exchanger. Ion exchanger undergoes reaction with the cations and anions of the surrounding solution respectively.

Sr.no	Drug	Technique	Coating agent	Dosage form
01	Acetaminophen Caffeine/cimetidine Ciprofloxacin Levofloxacin	Wurster fluid bed coating	Croscarmellose Eudragit RL 30D,RS3OD Eudragit NE30D/RL30D, HPMC Eudragit E100, cellulose Acetate	Dispersible tablet Chewable tablet Oily suspension sachets Suspension
02	Sildenafil citrate Chlorpheneramine maleate Dextromethorphan Hydro bromide	Top spray fluid bed coating	Eudragit NE30D, E-100 Ethyl cellulose PVP-K30	Mouth melt Tablet
03	Acetaminophen Theophylline	Tangential spray fluid bed coating	Eudragit E-100, Cellulose acetate Eudragit NE30D, guar Gum	Chewable tablet Dry Suspension
04	Ampicillin trihydrate Nizatidine Roxithromycin	Spray drying	Sodium CMC Eudragit E-100 Eudragit RS100/RL100	Powders Sprinkles Suspension
05	Clarithromycin	Spray congealing	Glycery lmonostearate, Eudragit E100	Powders
06	Chloroquine diphosphate	Coacervation phase Separation	Eudragit RS100	Powders
07	Metronidazole	Solvent Evaporation	Eudragit E, Fattibase	Dry Suspension
08	Diclofenac sodium	Wet agglomeration Coacervation	Ethylcellulose,toluene, Petroleum ether	Enteric coated tablets powders
09	Beclamide Microencapsulation Gelatin	Spray drying and spray congealing	Gelatin	Tablets powders

Table 4: Examples of Taste concealed bitter drugs by microencapsulation [19] [20][21][22]

Exchange capacity

The exchange capacity of IERs refers to the number of ionic sites per unit weight or volume (meq./gram or meq./mL). Sulfonic acid resin derived from polystyrene matrix has lower exchange capacities, about 4 meq/gms, than carboxylic acid resins derived from acrylic acid Polymer, about 10 meq/gms, because of bulkier ionic substituent of Sulfonic acid resin and Polystyrene matrix. Weak acid cation exchange resin have pKa value of about 6, so that pH4 or above their exchange capacity tends to increase. Ionization of weak acid cation exchange resin occurs to appreciable extent only in alkaline solution, i.e. in their salt form. This is reported that their exchange capacity is very low below pH 7 and moderately constant values at pH above about 9.The rate of ion exchange is influenced by the permeability of the solvent and solute through the pores of the resin, whose number and size are influenced by the amount of cross linking. The diffusion path length is obviously also related to the size of the resin particles.

Applications:

IERs are used in drug formulation to stabilize the sensitive components, sustain release of the drug, and taste masking. Interaction of amine drugs with polycarboxylic acid IERs indicated that these resins may be quite useful in taste coverage. These studies indicated that saliva with an average pH of 6.7 and a cation concentration of 40 meq/L would only elute a limited percentage of drug from adsorbate. However

rapid elution would occur as soon as the adsorbates are exposed to the low pH of the stomach. The particle coating of polycarboxylic acid IER adsorbates can also be considered as a method for achieving taste coverage.

5. Taste masking by formulation of inclusion complexes: [23,21]

Inclusion complexation is a process in which the guest molecule is included in the cavity of a host or complexing agent. The complexing agent is capable of masking bitter taste of drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to buds. Thereby reducing the perception of bitter taste. Van des Waals force are mainly involved in inclusion complexes. β –cyclodextrin is most widely used complexing agents for inclusion type complexes. It is sweet, nontoxic, cyclic oligosaccharide obtain from starch.

Strong bitter taste of carbepentane citrate syrup was reduced to approximately 50% by preparing a 1:1 complex with cyclodextrin. Palatable ibuprofen solutions are prepared by forming 1:11 to 1:15 inclusion complex with ibuprofen and hydroxypropyl β–cyclodextrin, respectively. The complex masked the bitter component but creates a sore taste that is masked by sweetness. Pharmaceuticals or food additives containing gymnima Sylvester, a bitter and astringent tasting. Sweetener for diabetes control can have the unpleasant taste masked by mixing with β –cyclodextrin further enhances the blood sugar lowering effects of gymnemic acids.

Type	Functional group	Matrix structure	Commercial resins	Taste masked drugs
Weak cation	-COOH	Methacrylic acid Divinylbenzene	Indion204, tulsion T-335,AmberliteIRC	Norfloxacin, ofloxacin Roxithromycin
	-COO-K+	Methacrylic acid Divinylbenzene	Tusion T339 Indion 234 AmberliteIRC88	Ciprofloxacin chloroquine
STRONG CATIONS	-SO3H	Divinylbenzene polystyrene	Indion244,Dowex50 AmberliteIR120	Chlorpheneramine ,maleate ,Ephedrine Hydrochloride
	-SO3Na	Sodium polystyrene Divinylbenzene	Tusion T-344 AmberliteIRP69 Indion 254	Dicyclomin Dextrometorphen, pseudoephidrene Buflomedil Ranitidine
WEAK ANIONS	N-R2	polystyrene Divinylbenzene	Amberlite IR4B Dowex 2	NTM
STRONG ANIONS	N-R2	polystyrene Divinylbenzene	Amberlite IR400 Dowex1 Indion454 Duolite AP143	NTM

Table 5: Some commonly used ion exchange resins. [24]

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sugar lowering effects of gymnemic acids.

6. Taste masking by granulation:[22]

Granulation is a common processing step in the production of tablet dosage form. This step can be exploited as a mean for taste masking of slightly bitter tasting drug. Some saliva insoluble polymers can also act as binding agent, granules

prepared from these polymers show less solubility in saliva and thus taste could be masked. Granulation lowers the effective surface area of the bitter substance that comes in contact with the tongue upon oral intake. But this reduction in surface area of bitter substance may or may not be effective in masking the bad taste. Taste masked granules, prepared from saliva insoluble polymer, can be formulated in various type of tablet dosage form. Example rapidly disintegrating tablets and chewable tablets. Taste masked granules of bitter tasting drug pirenzepine and oxybutynin have been prepared by the extrusion using aminoalkyl methacrylate copolymer. (EudragitE-100)

Drug(s)	Granulating Agent(s)	Percentage of Excipients	Comments
Erythromycin	Alginic acid	Drug : polymer Ratio of 2.5:1 to 50:1	Taste masked granules, which can be formulated as dry syrup suspensions/ chewable of dispersible tablets
Dextromethorphan	Cyclodextrin	Drug : polymer Ratio of between 0.9:1 and 1:25	Mixing of drug with Cyclodextrin followed by granulation; without complexation
Ibuprofen	Microcrystalline cellulose (MCC)	Ratio of drug to MCC is 70:30 to 90:10 w/w	Ratio of drug toMCC is 70:30 to90:10 w/w

Table 6: Examples of drugs taste masked by granulation technology [26]

7. Taste masking by adsorption: [27]

Adsorbates are commonly used in taste masking technologies. Adsorbate of bitter tasting drug can be considered as the less saliva soluble versions of these drugs. Adsorption involves preparing a solution of the drug and mixing it with an insoluble powder that will adsorb the drug, removing the solvent, drying the resultant powder, and then using these dried adsorbates in the preparation of the final dosage form. Many substrates like veegum, bentonite, silica gel and silicates can be used for the reparation of adsorbate of bitter drugs. The bitter taste of ranitidine is masked by forming an adsorbate with a synthetic cation exchange resin.

Drug	Adsorbents
Ranitidine	Magnesium trisilicate
Dextromethorphan hydrobromide	Magnesium trisilicate
Ttimethoprim	Magnesium aluminium silicate(veegum F)
Loperamide	Magnesium aluminium silicate(veegum F)
Phenyl propanol amine	Magnesium aluminium silicate(veegum F)

Table 7: Examples of drugs and adsorbent used in adsorption technique[23]

8. Taste masking by prodrug approach [28]

A prodrug is chemically modified inert drug precursor which upon biotransformation liberates

the pharmaceutically active parent compound. A combination of factors is perhaps operative in the demonstration of a taste response molecular geometry is one of them, for e.g., bitterness of a molecule, may be due to the efficiency of the taste receptor substrate adsorption reaction, which is related to the molecular geometry of the substrate. If alteration of the parent molecule occurs by derivative formation, the geometry is altered, affecting the adsorption constant. This effect, in turn, may or may not be due to lack of aqueous solubility of the derivative to eliminate the bitter taste response. Thus the magnitude of a bitter taste response or taste receptor-substrate adsorption constant may be modified by changing the molecular configuration of the parent molecule. The extremely bitter antibiotics have been the focus of much work in reversible drug modification

Parent molecules	Reversible modifications
Chloramphenicol	Palmitate or phosphate ester
Clindamycin	Alkyl ester
Erythromycin	Alkyl ester
Lincomycin	Phosphate or alkyl ester
Tetracycline	3,4,5-Trimethoxy benzoate salts

Table 8 : Prodrug for bitter taste masking

9. Taste masking by bitterness inhibitors [29]

The development of a specific universal inhibitor for bitter taste has been widely required in the fields of taste physiology and pharmaceutical sciences, but no such inhibitors has been available. One difficulty in discovering of universal inhibitor for bitter taste is that substances that inhibit bitterness of one compound will not influence the bitterness of a second because many different classes of compound impart bitterness. Sodium salts such as sodium chloride, sodium acetate, sodium gluconate have been shown to be potent inhibitors of some bitter compounds. The mechanism is not known, however, research shows

That sodium act at peripheral taste level rather than a cognitive effect. Bitter substances are commonly hydrophobic in nature hence lipoprotein (PA-LG) composed of phophatidic acid and β-11lactoglobulin can mask the target sites for bitter substances on the taste receptor membrane without affecting responses to salts, acids, sugars or sweet amino acids. Bitter taste of brucine, berberine, chloride, caffeine, denatonium benzoate, glycyl L-leucine, L-phenylalanine, naringin, propranolol hydrochloride, quinine hydrochloride, strychnine nitrate and theophylline have been suppressed by lipoprotein. Selective inhibition of bitter taste of various drugs by phospholipids such as phosphatidic acid, phosphatidylinositol, soy lecithin, has been reported. Bitter tastes of polymixin B sulphate and trimethoprim, sulfamethoxazole have been masked by BMI obtained by fractionating soy lecithin. The w/o/w or o/w/o type multiple emulsions are vesicular systems in which active ingredients can be entrapped in internal phase. The entrapped substances can be transferred from internal phase to external phase through the 'membrane phase'. This phase controls the release of drug from system. This system could be used for controlled-release delivery of pharmaceuticals. If the system is stable enough for a reasonable shelf life, the formulation could also mask the taste of drug. Both w/o/w or o/w/o multiple emulsions of chloroquine phosphate

Have been prepared and reported to be partially effective in masking the bitter taste of drug.

10. Multiple emulsions.[30]

Multiple emulsions are complex poly dispersed systems where both oil in water and water in oil emulsion exists simultaneously which are stabilized by lipophillic and hydrophilic surfactants respectively. The ratio of these surfactants is important in achieving stable multiple emulsions. Among water-in-oil-in-water (w/o/w) and oil-in-water-in-oil (o/w/o)type multiple emulsions; the former has wider areas of application. The formulation is designed to release the drug through the oil phase in the presence of gastrointestinal fluid.

Example: polyvinyl acetal diethyl amino acetate microspheres containing trimebutine .

To produce acid soluble, polyvinyl acetal diethyl amino acetate microspheres containing trimebutine (as maleate) using a water-in-oil-in-water (w/o/w) emulsion solvent evaporation method is used to characterize their in-vitro release properties. The pH of the external aqueous phase was the critical factor in achieving a high loading efficiency for trimebutine in the microencapsulation process; nearly 90% (w/w) loading efficiency was obtained at above pH 10. Trimebutine was completely released from AEA microspheres within 10 min in a dissolution test at pH 1.2, simulating conditions in the stomach, whereas at pH 6.8, the pH in the mouth, only small quantities of trimebutine were released in the initial 1–2 min. The results of a gustatory sensation test in healthy volunteers confirmed the taste-masking effects of the AEA microspheres. Finally, an attempt was made to encapsulate the

salts of other basic drugs (lidocaine, imipramine, desipramine, amitriptyline, promethazine and chlorpheniramine) into AEA microspheres using the w/o/w emulsion evaporation method. The loading efficiencies were ranked in almost inverse proportion with the solubility of the drugs in the external aqueous phase. This study demonstrated the possibility of masking the taste of salts of basic drugs by microencapsulation with AEA using a w/o/w emulsion solvent evaporation method

11. Solid dispersion system [31]

Solid dispersion have been defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting (fusion) solvent or melting solvent method. Carriers used in solid dispersion system include povidone, polyethylene glycols of various molecular weights, hydroxyl propyl methyl cellulose, urea, mannitol and ethyl cellulose. Various approaches for preparation of solid dispersion are mentioned below:-

Melting method, *Solvent method* and *Melting solvent method*.

Drug	Polymer	Result
Refecoxib	Poloxamer-188	Melting method is used
Artemether	Mono amino glycyrrhyzinate pentahydrate	Formulated tablets are prepared

Table 9: Taste masking by solid dispersions [20]

12. Molecular complexes of drug with other chemicals [28]

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 pitman, 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

13. Taste masking by gelation [32]

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. Tablet of amiprolose hydrochloride have been taste masked by applying an undercoat of sodium alginate and overcoat of calcium gluconate. In presence of saliva, sodium alginate reacts with bivalent calcium and form water insoluble gel and thus taste masking achieved.

14. Using Liposome [33]

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-hydroxyetylpiperzine-N'- 2- ethane sulfonic acid) buffer at pH 7.2

15. Mass Extrusion Method (Dispersion Coating) [34]

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.

16. Salts or derivatives: [35]

In this approach, an attempt is made to modify the chemical composition of the drug substance itself, so as to the taste buds. Aspirin tablets can be rendered tasteless by making magnesium salt of aspirin. D-chlorpheniramine maleate is taste-masked salt of chlorpheniramine. The alkyloxy alkyl Carbonates of Clarithromycin have remarkably viated bitterness and improved bioavailability when administered. Sodium salts such as sodium chloride, sodium acetate, sodium gluconate have been shown to be potent inhibitors of some bitter compound. The mechanism is not known, however, research shows that sodium act at peripheral taste level rather than a cognitive effect.

17.Amino Acids and Protein Hydrolysates [36]

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

18. Miscellaneous taste masking approaches

Use of by effervescent agents [37]

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have been employed for use as taste masking agents for dosage forms that are not dissolved in water prior to administration. A chewing gum composition of bitter medicament

was formulated to supply the medicament to oral cavity for local application or for buccal absorption. It comprise a chewing base, an orally administrable medicament, a taste masking generator of carbon dioxide, and optionally a taste bud desensitizing composition (e.g., oral anesthetic such as benzocaine) and other non-active
material such as sweeteners, flavouring components, and fillers. Recently, effervescent tablets of fentanyl and prochlorperazine were developed to supply these drugs to the oral cavity for buccal, sublingual, and gingival absorption. The formulations contain the drug in combination with effervescent agent to promote their absorption in the oral cavity and to mask their bitter taste. An additional pH adjusting substance was also included in fentanyl formulation for further promotion for absorption

- ***Rheological modification*** [38,35]

Increasing the viscosity with rheological modifier such as gums or carbohydrates can lower the diffusion of bitter substances from the saliva to the taste buds. Acetaminophen suspension was formulated with xanthene gum (0.1-0.2%) and microcrystalline cellulose (0.6-1%) to reduce bitter taste. The antidepressant drug mirtazapine is formulated as an aqueous suspension using methionine (stabilizer) and maltitol (thickening agent). Maltitol is stable in the acidic pH range of 2 to 3 and besides, it masks the unpleasant taste of the drug. It also inhibits the undesirable local anesthetic effect of the drug.

- ***Continuous multipurpose melt (CMT) Technology*** [20]

The CMT method was developed for the continuous granulation and Coating of pharmacologically active substance

- ***Hot melt coating***

Polymer coating are widely used to provide drug protection, taste masking, coloration and modified drug release. Typically, coating polymers must be diluted or dispersed in solvents (water or organic) prior to coating and gliding agents are commonly added to prevent particle sticking throughout processing. Lipid excipients present an attractive alternative to standard polymer coatings as they only require melting before application directly onto the substrate. Solvent evaporation is not required; consequently powders with very high specific surface areas can be coated rapidly. A number of different lipid excipients can be used in coating and choosing the appropriate excipients for the application requires an understanding of their physico-chemical properties and its associated effect on drug release.

Evaluation techniques [23]

Taste is a very subjective perception. Depending on individuals, the perceived taste may vary to different degrees. Still, well controlled experimental set up, can accurately and reproducibly measure taste thresholds. To quantitatively evaluate taste sensation, following methods have been reported in literature

1. Panel testing (human subjects)
2. Measurement of frog taste nerve responses.
3. Multichannel taste sensor/ magic tongue
4. Spectrophotometric evaluation/ D30's value

- ***Panel Testing***

This method involves taste comparison between test and reference solutions by a group of about 5-10 human volunteers. Reference solutions vary 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. This method is easy accompanied with the accuracy of human perception of taste against any other gustatory evaluation technique

- ***Measurement of Frog Taste Nerve Responses***

In this method, adult bull frogs are anaesthetized intraperitoneally and the gloss pharyngeal nerve is then located and dissected from the surrounding tissue and cut proximally. Anac-amplifier and an electronic integrator are used to respectively amplify and integrate the nerve impulses. The peak height of the integrated response is then taken as the magnitude of response. Quinine sulphate formulations, tastes masked by PA-LG (phosphatidic acid-lacto globulin) combination have been reported to be evaluated by this technique

- ***Multichannel Taste Sensor / Magic tongue***

This is an automated taste sensing device to detect the magnitude of bitterness of a 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 a manner similar to human gustatory sensation. Taste response is transferred into pattern composed of electric signals of membrane potentials of the receptor part. Different response electric potential pattern are obtained for substance producing different taste qualities

Recently, the technique has been applied, for the quantitative evaluation of the bitterness of some commercially available medicines containing

quinine, diclofenac sodium, salicylic acid, theophylline, caffeine and metronidazole

- ***Spectrophotometric Method***

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, 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*. This technique has been applied to evaluate the taste masked granules of sparfloxacin, with Threshold concentration being 100µg/ml

RECENT TRENDS [39,40,41,42]

AdvaTab ODT Technology

Advatab ODT Technology is developed by APTALIS Pharmaceutical technologies. Various advantages offered by this technology include high physical stability, stability during package and transport, pleasant taste (with Microcap technology) and good patient compliance.

Microcap ODT Technology

Microcap ODT technology is developed by APTALIS Pharmaceutical technologies. This technology uses coating method for taste masking. The polymeric membrane eliminates the unpleasant taste and or odor. Offer advantages like precise taste masking, good release profiles and patient compliance.

Liquitard ODT Technology

This sophisticated Liquitard technology is developed by APTALIS Pharmaceutical technologies with an aim to provide an effective, convenient, ready-to-use, taste-masked powder formulation in single dose sachets that can be administered as a suspension or sprinkle on easy to swallow foods. This is developed with a wide variety of flavors and is compatible with customized release profiles.

Formulplex and Formulcoat

Pierre Fabre developed a new taste masking technologies in which, coating of micro or nanosized particles at room temperature with non organic solvent.

KLEPTOSE® Linecaps

Roquette offers a new taste-masking technology: KLEPTOSE® Linecaps, uses a pea maltodextrin for masking the bitter taste of drugs by decreasing the overall amount of drug particles exposed to the taste buds.

CONCLUSION

Taste masking is a viable strategy to improve the patients compliance, especially for bitter drugs whereby, a gamut of methodologies may be adopted to deliver a palatable formulations taste masked products developed from innovative pharmaceutical technologies not only increase the commercial profit but also create brand value for a company.

After considering all these factors it is concluded that an ideal taste masking formulation should have following properties.

- Involves least no. Of equipments and processing steps.
- No adverse effects on drug bioavailability
- Require minimum no. Of excipients for an optimum formulations .
- Require excipients that are economical and easily available .
- Require excipients that have high margin of safety .
- Rapid and easy to prepare

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