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TASTE MASKING: MOST COMMON TECHNIQUES USED IN PHARMACEUTICAL INDUSTRY

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ABSTRACT

There is four primary taste sensation which pose difficulty with the acceptability of oral drugs: bitter, sour, sweet and salty taste. the bitter taste is the one most accused of formulation problems due to its low threshold concentration. to remedy this situation, several taste masking techniques have been developed by playing with various parameters such as the decrease in the solubility of the drug in contact with saliva or the decrease in its surface of contact with taste buds. These techniques include adding of sweeteners, flavouring agents, use of granulation, microencapsulation, coating agents, complexing agents, ion exchange resins, viscosity enhancers and formation of prodrug and solid dispersion. The aim of this paper is to review the most methodologies and taste masking techniques used in pharmaceutical industry.

KEYWORDS: Taste masking techniques, bitter drugs, taste buds, selection criteria.

INTRODUCTION

Taste is one of the most important parameters that condition patient compliance, especially for pediatric and geriatric patients. Undesirables and particularly bitter taste are among of several formulation problems observed with oral dosage form. Four taste sensation are confirmed to specific regions of tongue: bitter, sour, salty and sweet taste. The threshold concentration of a substance that evokes perception of bitter and sour taste is very low in comparison with sweet and salty substance.[1] Taste transduction involves the interaction of molecule with taste buds through distinct mechanisms. Each taste bud transmits information about the substance taste to the central nervous system **"fig. 1"**. There is an important connection between the molecular weight and the taste sensation of drug. More the molecular weight of substance drug is higher more it tends to be bitter while the Low molecular weight substances tend to be salty. The sweet and salty taste caused by some organic compounds such as alkaloids and sucrose, are transduced by G protein gustducin while for salty and sour taste respectively caused by inorganic compounds such as sulphate and acid salts such as sodium bicarbonate, its transduction is mediated by ion channels.[2,3]

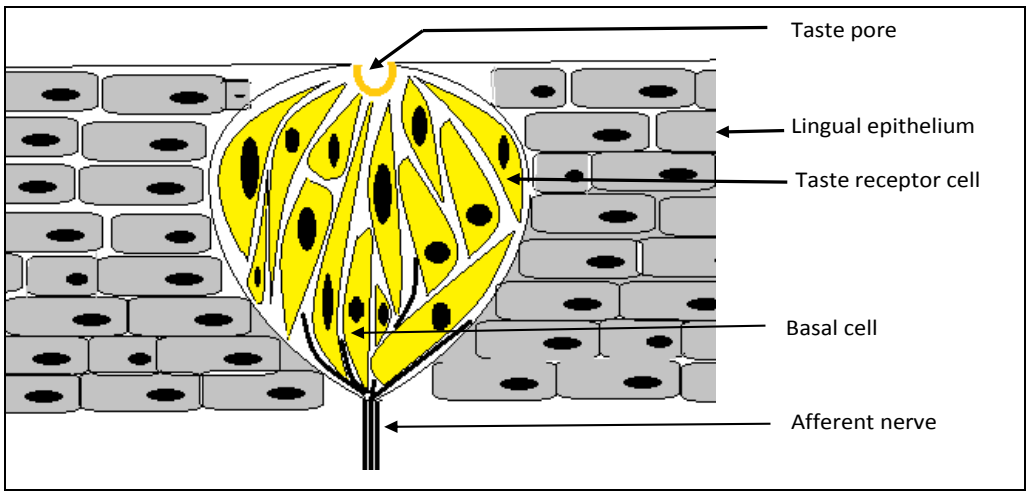


Figure 1: taste buds structure.

Table 1 shows us the threshold concentrations of substances that evoke taste perception.

Table 1: Threshold concentration of primary taste sensation.[4]

Sr. No.	Taste sensation	Threshold concentration (%)
1.	Sweet (sucrose)	0.5
2.	Sour (HCL)	0.25
3.	Salt (NaCl)	0.007
4.	Bitter (quinine)	0.00005

The sensibility of tongue to primary taste sensation is variable. The bitter taste is respectively 10000, 5000 and 140 time higher than sweet taste, sour taste and salt taste. The purpose of this evaluation carried out by GUYTON C. et al.[4] was to determine the taste sensation that poses the most several problems in formulation drugs.

The mechanism of most taste masking techniques used in pharmaceutical industry are based either on the reduction of the solubility of substance in saliva, so that its concentration in saliva remains below the threshold concentration of taste[5,6], or on alteration of the interaction of substance with the taste cells, thereby promoting the acceptability of the drug by the patient.[6]

PHARMACEUTICAL METHODS AND AGENTS USED IN TASTE MASKING

Different approaches and agents are used to overcome the problem of undesirable taste of some drugs. These techniques serve not only to mask the taste but sometimes to improve the odor and bioavailability of the drug.

Flavouring and sweetening agents

Using flavouring and sweetening agents is the simplest taste masking technique usually used for slightly bitter substance because of its inefficiency for highly unpleasant taste and highly water-soluble drugs. It is generally used for oral liquid dosage forms intended for pediatric populations.[7] This approach can be used alone or in association with other taste masking technique in order to improve its efficiency.[7,8]

Being very soluble in water, sweeteners dissolve in saliva and coat the taste buds, delaying the interaction of bitter substance with the taste buds. They improve the perception of taste without changing the concentration of free drug substance. The **table 2** gives us a compilation of the most sweeteners used in pharmaceutical industry:

Table 2: List of the most used sweeteners in the pharmaceutical industry.

Sr. No.	Sweetening agent	Relative sweetness	Comments	Solubility
1.	Acesulfame potassium	137-200	Bitter in higher concentration	Slightly soluble in ethanol
2.	Glycyrrhizin	50	Moderately expensive	Soluble in water and alcohol
3.	Mannitol	0.6	Negative heat of solution	Soluble in alkali
4.	Saccharin	450	Unpleasant after taste	Rapidly soluble in dilute ammonium solution
5.	Sucrose	1 (standard)	Most commonly used	Soluble in water
6.	Stevia	300	Artificial sweetener	Soluble in water and ethanol
7.	sucralose	600	Synergistic sweetening effect	Freely soluble in water, ethanol and methanol

While the flavouring agents reduce the bitterness perception of drug product and improve it taste by numbing taste buds achieved with the freshness effect accumulated and felt after the administration of the product without any real increase in the temperature of the tongue.[5,9]

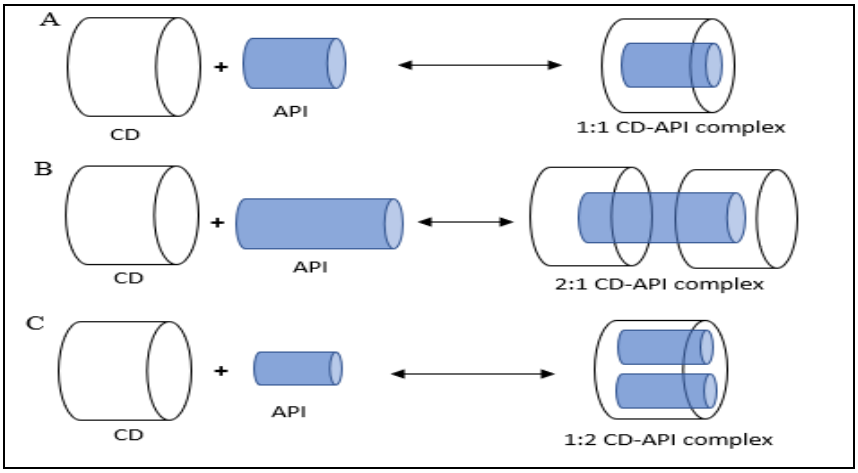
Some combination of flavouring agents and the primary taste sensation of tongue are recommended.[5,10] **The table 3** gives us some examples of flavours usually employed to mask salt, bitter, sweet and sour taste.

Table 3: Choice of flavouring agents according to taste sensation of drug substance.[11]

Sr. No.	Taste sensation	Recommended flavour
1.	Salt	Butterscotch, peach, apple, vanilla
2.	Sweet	vanilla and berry
3.	Bitter	Walnut, cherry, mint, chocolate
4.	Sour	Raspberry, citrus, licorice

Inclusion complexes

Taste masking by formation of inclusion complexes is one of the techniques widely used to mask the unpleasant taste of the active substances, and which has the beneficial advantage of improving their solubility. Inclusion complex is a "host-guest" relationship in which the complexing agents is the host and the active ingredient is considered as the guest thereby decreasing the amount of substance exposed to the taste buds.[6,12] The complexing agents act by modifying the biopharmaceutical parameters of the drug such as dissolution. The most commonly used complexing agent is cyclodextrin. It is a cyclic and nontoxic oligosaccharide derived from starch, having hydrophobic poles in the middle of their cavity and hydrophilic poles on the external surface.[13] The number of molecules included in the host molecule depends mainly on the molecular weight of the guest molecules **"fig. 2"**. For low molecular weight molecule more than one guest molecule can be included in the cavity, but for high molecular weight molecule more than one host molecule may bind to the guest.[14,15]



Note: CD; cyclodextrin, API; Active pharmaceutical ingredient.

Figure 2: Representation of drug inclusion complexation with cyclodextrin. (A) Reception of one API molecule in cyclodextrin cavity. (B) Case of hight molecular weight API. (C) Case of low molecular weight API.

Several studies have focused on the formation of inclusion complexes to reduce bitterness of drug product as shown on the **table 4** below.

Table 4: Various complexing agents used for improving taste of drug substance in literature.[13,16-20]

Drug	Complexing agents used	category
Dicyclomine hydrochloride	ß-cyclodextrin	Antispasmodic
Ranitidine hydrochloride	2-hydroxypropyl-ß-cyclodextrin	H_2 blockers
Cetirizine dihydrochloride	ß-cyclodextrin	H_1 Antihistaminic
Zinc acetate dehydrate	Aneththol-ß-cyclodextrin complexand saccharin	Recover zinc deficiency
Metronidazole benzoate	ϒ-cyclodextrin	Antibacterial
Ibuprofen	Hydroxypropyl- ß-cyclodextrin	NSAID
Diltiazem hydrochloride	ß-cyclodextrin	Calcium channel blocker
Gymnema sylvestre	ß-cyclodextrin, chitosan	Anti-diabetic
Hexitidine	ß-cyclodextrin	Antibacterial
Benexate hydrochloride	ß-cyclodextrin	Antiulcer
Carbetapentane citrate	cyclodextrins	Local anesthetic
Zipeprol	ß-cyclodextrin	Antitussive
Famotidine	ß-cyclodextrin	H_2 blockers
Levosulpiride	ß-cyclodextrin	Antipsychotic
Chloroquine phosphate	Tannic acid	Antimalarial
Dimenhydrinate	Eudragit-S-100	Antiemetic
Guaiacol	ß-cyclodextrin	Antidiarrhetic

Ion exchange resins

Ion exchange resins are inert polymers made up of a network of hydrocarbons to which ionizable groups are linked. The charge of functional groups determines the type of resin: cationic or anionic resins. These ion exchange resins have the possibility to lose their mobile

ions to fix ions of similar charge of the active substance in order to form less bitter drug[21,22], that mean the molecules of the active substances are attached to the resin substrate to form insoluble adsorbates using weak van der Waals bonds so that the resin-PA complex will not dissociate under the action of saliva.[7] The exchange capacity of this complex depends to the number of ionic sites per volume or weight, it can be expressed in meq/g ou meq/ml.[5]

Ion resins exchange are classified in four groups according on the nature of functional groups attached to the resin substrate.[23]:

- Strong acid cation exchange resin with sulfonated groups
- Weak acid cation exchange resin with carboxyl groups
- Strong base anion exchange resin with quaternary ammonium groups
- Weak base anion exchange resin with amino groups

The **table 5** below shows us some examples of ion exchange resins used for taste masking of ionic drugs:

Table 5: Examples of taste masking by ion exchange resins.[24]

Drug	Commercial resin	Type	Functional group
Etoricoxib	Indion 204	Weak acid cation exchange resin	Carboxylic acid
Ciprofloxacin, Chloroquin phosphate	Indion 234	Weak acid cation exchange resin	Carboxylic acid
Ranitidine	Amberlite IRP 69	Strong acid cation exchange resin	Sulfuric acid
Metronidazole	Kyron T-134	Weak acid cation exchange resin	Carboxylic acid
Azithromycin	Idion 214	Weak acid cation exchange resin	Carboxylic acid

Granulation

Granulation is a process that involves decreasing the specific surface area of the bitter substance molecules in contact with the taste buds[25], allowing small particles to assemble into larger ones. It is a fast technique, easy to implement and inexpensive, in which insoluble polymers in saliva and low melting point waxes can be used as binding agents.[25,26] It is generally used for slightly bitter substances.[27]

Table 6 presents examples of taste masking of bitter drug by granulation:

Table 6: Examples of taste masking by granulation.[22,28,29]

Drug	Category	Granulating agents used
Erythromycin	Macrolide	Alginic acid
Dextromethorphan	Antitussive	Cyclodextrin
Norfloxacin	Flouroquinolone	Methacrylic acid ester
Satranidazole	Stearic acid	Nitroimidazole
Ibuprofen	Anti-inflammatory	Microcrystalline cellulose (MCC)
Levofloxacin	Flouroquinolone	Castor oil, sugar alcohol
Amoxicillin trihydrate	Betalactam	L-HPC, MCC
Vitamins	Diet supplement	Polyglycerol ester of polyvalent fatty acids

Note: L-HPC; low substituted hydroxypropyl cellulose, MCC; microcrystalline cellulose.

Microencapsulation

Microencapsulation is a process which is based on imprisonment in polymer film, very small droplets of liquid or solid particles. This technique reduces the solubility of active ingredient (API) in saliva. The microcapsules thus formed are mixed with the other excipients. The resulting drug product flavour is that of the soluble constituents only.[30,31] The interfacial polycondensation, coacervation, solvent evaporation, spray drying and spray congealing are the most techniques of microencapsulation used for drug product taste masking intended to be administered orally.[5] **The table 7** gives some examples of API using these techniques to hide their better taste:

Table 7: Examples of taste masking by microencapsulation.[30]

Drug	Category	Polymer for microencapsulation	Technique
Ampicillin trihydrate	Betalactam	Sodium CMC	Spray drying
Nizatidine	H_2 Blockers	Eudragit E 100	Spry drying
Clarythromycin	Macrolides	Glyceryl monostearate	Spray congealing
Chloroquine diphosphate	Amino-4-quinolines	Eudragit RS 100	Coacervation phase separation
Metronidazole	Nitro-5-Imidazole	Eudraget E, Fattybase	Solvent evaporation

Polymers to be used must be able to mask the taste without modifying the API release profile.[25,26] To ensure this balance, a combination of water-soluble polymers such as cellulose acetate butyrate and povidone, and pH independent insoluble polymers such

as cellulose ester and polyvinyl acetate is recommended.[25]

Coating

It is considered as one of the most common and effective technologies used for taste masking. It consists in forming a physical barrier of one or more layers of polymers between the bitter product and the taste buds, which minimizes the interaction between them.[7]

Hydrophobic polymers, lipids, hydrophilic polymers and sweeteners are used as coating agents. The choice of the appropriate combination of coating agents conditions the maintenance of equilibrium between the taste masking by decreasing the solubility of PA in the oral cavity and its expected release profile.[7,25,26] The polymer coating used for taste masking can be beneficious at the same time to protect hygroscopic drugs from moisture or to modify the release profile of the drug. **Table 8** shows examples of coating agent used for taste masking:

Table 8: Examples of taste masking by coating.[8,32-34]

Drug	category	Coating agent
Nicorandil	vasodilator	Croscarmellose sodium
Ibuprofen	anti-inflammatory	Eudragit L300, propylene glyol, mannitol and flavour
Pinaverium bromide	antispasmodic	Cellulose or shellac
Propantheline bromide	Antimuscarinic	Ethyl cellulose, L-HPC
Amiprilose HCL	anti-inflammatory	Calcium gluconate and sodium alginate

Note: L-HPC; low substituted hydroxypropyl cellulose.

Prodrug approach

A prodrug is a substance administered in an inactive or incompletely active form, but which converts to its active form by a normal metabolic process.[35] It is an effective approach that acts by decreasing the solubility of the substance and consequently decreases the magnitude of the receptor-substance adsorption reaction. This technique is widely used for very bitter antibiotics **(Table 9)** and opioid analgesic.

Table 9: Examples of taste masking by produg approach.[5,12]

Drug parent	Prodrug	Category
chloranphenicol	Palmitate ester of chloranphenicol	Phenicols
Theophiline	7-7' Succinylditheophiline	xanthine derivatives
Erythromycin	Lauryl sulfate Salt of erythromycin estolate	Macrolides
Clindamycin	Clindamycin-2 palmitate	Macrolides
Tetracycline	Tetracycline 3,4,5-Trimethoxybenzoate salt	Cyclins

Solid dispersion[6,10,30,36]

Solid dispersion is a technique used in taste masking that based on dispersion of one or more bitter API in an inert matrix (ex. Acrylic acid, Shellac, hydroxymethylcellulose…) at solid state. This dispersion can be achieved by different methods: melting method, solvent method and melting solvent method.

- Melting method: the solid dispersion is carried out by cooling of the mixture API- carriers previously melted, with an energetic stirring.
- Solvent method: the solid dispersion is based on the dissolution of the mixture API-carriers in a common solvent, followed by solvent evaporation.
- Melting solvent method: the solid dispersion is produced by mixing the carrier melted under the effect of the temperature and API in solution.

Viscosity enhancers

Increasing viscosity with rheology modifiers acts on 2 levels. it acts by decreasing the contact surface of the bitter substance with the taste buds, in the same time it retards the solubility of the bitter substance in saliva by delaying its migration.[7]

EVALUATION TECHNIQUE

Taste perception is very subjective, it can vary to different degrees according to each individual. Different quantitative methods in vitro and in vivo can be used to evaluate perceived taste:

In vitro approaches

a. Panel testing

The human panel testing is psychophysical evaluation of taste perception by a group of 5 to 10 of healthy volunteers with organoleptic sense. This group is trained for taste evaluation by using reference solutions. The test is performed by placing the product in mouth for 1 minute and evaluated using scale ranging from 0 tasteless to 5 very bitter product.[27,37]

b. Measurement of frog taste nerve responses

This technique measures the effects of taste stimuli of bitter product on frog taste nerve responses. The glossopharyngeal impulses of adult bullfrogs nerve were amplified by AC amplifier and integrated using electronic integrator. The intensity of impulses corresponds to the peak height of obtained response. The mouth must be pretreated by lipoprotein PA-LG

composed of phosphatidic acid and beta-lactoglobulin before placing the product to be tested.[38]

In vivo approaches

a. Multichannel taste sensor

This is an automated device which simulate an artificial tongue allowing to determine the intensity of bitter taste of the drug product tested.[26] This device recognizes, analyses, transduces and evaluates levels of taste and flavour. Taste response is transferred as electric signals that will be amplified and detected on a computer by statistical software.[37]

b. Spectrophotometric method

This method consists of diluting a known quantity of the substance to be evaluated in distilled water and then determining its concentration after filtration by spectrophotometry. the bitter taste of the drug is effectively masked when the determined concentration is below the threshold concentration.[39]

SELECTION CRITERIA OF TASTE MASKING TECHNIQUE

The choice of the appropriate technique depends on several factors which may be mainly related to the physicochemical properties of API **"fig. 3"** but also of the dosage forms of the technique chosen.

Extent of API bitterness

The extent of API bitterness may condition the choice of taste masking technique which means that more API is bitter more it requires efficient techniques. For example, sweeteners and flavouring agents may not achieve alone taste masking of highly bitter substance, but other techniques like coting or granulation can be used.

Dose of API

Dose of drug can guide the choice of technique which would be suitable to achieve taste masking. More dose is smaller like in pediatric formulations, more we can use simple techniques. For example, Formulation of perdiatric aspirin was developed by adding sweeteners, but this approach cannot work for higher dose aspirin formulations.[40]

Size and shape of drug particle

Particles shape and size distribution affect directly taste masking techniques efficiency. For example, drug with fine particles and irregular shape could decrease the efficiency of taste masking process used and varies the dissolution rate of the coated particles.[24]

Ionic characteristic of drug

For ionic Drugs, the ionic characteristics guide the choice of the ion exchange resins polymers to be used. anionic drugs need cationic polymers whereas cationic drugs require anionic polymers.

Drug solubility

More the drug is water-soluble more it will be in contact with the taste buds and therefore require more complex techniques to mask the bitter taste of API. Certain techniques such as taste masking by inclusion make it possible to improve both the perception of taste and the bioavailability of the drug.[41]

Dosage forms

The dosage form also can affect the choice of the taste masking techniques. For example, sweeteners, flavouring agents, microencapsulation and granulation are used in the formulation of chewable tablets alone or in combination with techniques such as viscosity enhancers for liquid formulations. While the coating is mainly used for dry formulations.

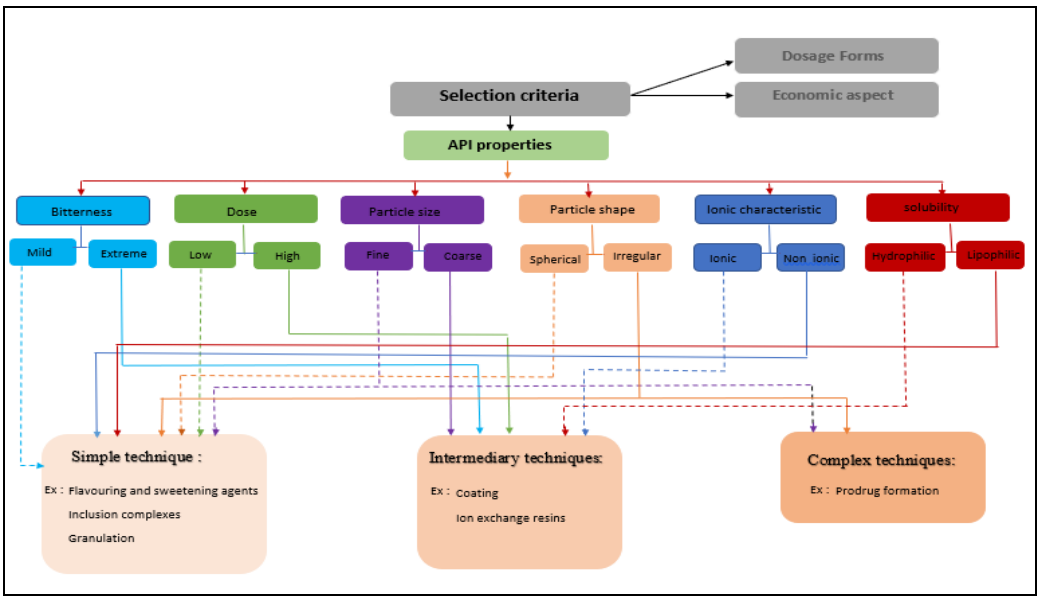


Figure 3: The active ingredients properties affecting the selection of taste masking techniques.

Selection of suitable taste masking techniques depend not only on the factors mentioned above but also on the economic aspect of each technique. simple techniques are generally more economical than intermediate and complex techniques.

CONCLUSION

Taste masking practice present one of the most important technology in pharmaceutical industry which directly impact the acceptability of bitter drugs by patients, especially in pediatric and geriatric populations thereby improving the quality of treatment. New techniques have been developed over the past decade to remedy the problems of the bitterest drugs and to optimize their formulations.

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