Taste masking techniques – A review

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ABSTRACT

The oral routeof administration is used for typically all type of formulations like tablets, capsules, powders, emulsions, and syrups. Unpleasant taste is the main concern for completing treatment in pediatrics. Bad taste is the key failures of oral dosage regime. In order to overcome this problem, various taste masking techniques are used to mask bitter active pharmaceutical ingredient (API). This article reviews various taste masking techniques and their evaluation test.

1. Introduction

Pharmaceutical formulations show the effective response of taste which is bitter in nature and it's the biggest barrier to patient compliance. There are several ways to administer the drug into an organism but oral route is most convenient, easy acceptable and cheapest available route for all class of drugs in geriatrics as well as pediatrics. The oral routeof administration is used for typically all type of formulations like tablets, capsules, powders, emulsions, and syrups. Unpleasant taste is the main concern for completing treatment in pediatrics. Bad taste is the key failures of oral dosage regime. In order to overcome this problem, various taste masking techniques are used to mask bitter active pharmaceutical ingredient (API). This article reviews various taste masking techniques and their evaluation test. Highly bitter drugs are quinine and celecoxib. Commonly utilized approaches for masking taste of drugs are reduction of solubility of drugs and reform the identity of the drug by combination with taste receptor [1].

1.1 Taste Perception

Taste is a sensation of flavour professed in the mouth and throat on contact with a substance. Taste buds (taste cells) present on tongue sense different tastes. On the average, human tongue has 2,000–8,000 taste buds. There are five basic tastes that have been known: bitter, salty, sweet, and sour and umami, out of which most API's are bitter in taste. Tastants stimulate the sense of taste. Tastants a ligand which binds to a receptor protein present on the plasma membrane of the taste receptor and stimulation of taste is transferred through cranial nerve IX to the brain. The conduction of signal of taste done by a process called taste transduction [2].

Table 1

Fundamental Sensation of taste [1]

Taste	Area Of Tongue
Sweet	Tip
Sour	Sides
Bitter	Back

1.2 Type of Taste [1, 3]

1.2.1 Sweet

Sweetness is mostly common which apparent during eating foods rich in sugars. Sweet is a sence of tastes are regarded as a pleasing experience, except perhaps in excess. Fructose is sweeter than sucrose and glucose. Polyhydric alcohols compounds containing -CH_2OH groups responsible for imparting a sweet taste.

1.2.2 Sour

The common food items which have natural sour taste is fruit, such as tamarind orange, lemon, grapes and melon. Wine also has a sour tinge to its flavour, and if not kept properly, milk can spoil and can develop a sour taste. Sourness is a taste can detect acidity. The sourness is an rated relative to dilute HCL acid, which has a sourness index of one. By differentiate; tartaric acid has a sourness index of 0.7, carbonic acid an index of 0.06 and citric acid an index of 0.46.

1.2.3 Bitter

Bitterness is sensitive of the tastes, which make sharp, unpleasant or disagreeable, but sometimes its desirable and by design added via various bittering agents. The compounds containing the esters of lactones, aromatic acids, and sulfur can exhibited bitterness. Most API's are bitter in taste due to salts of inorganic and organic compounds.

1.3 Task Masking Techno1ogies

1.3.1Addition of flavouring and sweetening agents

Most commonly used taste masking technique. These agents areaddedtoAPI which masks thebitter taste.Sweetening agents are alienated into synthetic and natural on the basis of origin. Synthetic sweeteners such as saccharin sucralose and aspartame show better progress in taste masking than the natural ones. In order to diminish taste perception of sweetening agents, they are added with alcohols like sorbitol, mannitol, and lactose. Sucralose used with an acid such as citric acid in the mandate to raise the taste masking efficacy of sweetener. Every sweetener has its own specific taste masking efficiency and shows the value of sweetness compared to standard (sucrose) [1, 4].

Table 2:

Example commonly use sweeteners and their relative sweetness [1]

Sweeteners	Relative sweetness	Significance
Lactose	0.16	Required in higher quantity
Acesulfame potassium	137-200	In more quantity bitter in taste
Aspartame	200	It is less soluble in solution
Saccharin	450	Unpleasant taste after take
Sucralose	1	Mostly used
Glycyrrhizin	50	Expensive
Sucralose	600	Synergistic sweet effect
Cyclamates	40	Banned product
Mannitol	0.60	Show the negative heat of solution

Flavouring agents are used for to mask the taste of drugs. They are classified as natural and synthetic respectively. Eucalyptus oil is most commonly used in cough syrup formulations. These agents contribute cooling effect after taste perception. Usage of flavouring agent depends on its compatibility with the drug [1].

Table 3

Example of taste masking by the addition of sweeteners and flavours [1]

Taste of drug	**Taste masking agent**
Eucalyptus oil	Borneol, Fenchone,
Ibuprofen	Sucrose, Saccharin sodium, sorbitol
Riclosan, Thymol	Limonene ,Citrus flavour
Zinc acetate dehydrate	Saccharin sodium
Guaifenesin, Acetaminophen, and Dextromethorphan hydro-bromide	Citric acid , Citric acid, Sucralose
Proteins and Amino-acids	Sacral
potassiumguaiacol sulfonate, Dihydrocodeine phosphate	Liquorice, Aspartame, and Saccharin sodium
Levofloxacin	Sucralose, Saccharin sodium, Aspartame
Acetaminophen / Aspirin	Sucralose, Aspartame, and Menthol
Iron compounds	Xylitol, Sorbitol, Sucralose, Mannitol or Erythritol
Mineral supplements	Acesulfame potassium Glycyrrhizin
Vegetable crude drug	Caramel
Vitamins	Cocoa powder, Aspartame, Stevia extract
Pseudoephedrine	PEG with Sucralose

1.3.2 Coating

This is the process in which API's coated with excipients which prevent the interaction of taste buds with drugs for a limited period of time and helps in swallowing of tablets. The coating agent acts as physical barriers and entangled drug particles. They are divided into sugar, lipids, and polymers. Generally, polymers are used for to mask the taste. Taste masking of bitter drugs by coating is the most effective method.

Polymers are also divided into water soluble and water insoluble. Lipids, polymers, and sugar can be used as a combination to achieve better taste masking by forming multiple coating layers. The commonly used excipients for coating are methyl-cellulose, hydroxypropyl methylcellulose, ethyl-cellulose, starch and gelatine, acidic compounds like malic and citric acid, water soluble organic acids are used as polymers. Different techniques of the coating are adopted to reduce coating imperfections like fluidized bed coating, air suspension technique for microcapsule. Types of coating include: film coating, enteric coating and press coating, examples are given in the table below [1].

Table 4

Literature report on taste masking by coating [1]

Nature of polymer	Examples
WSP*	Hydroxyl ethyl cellulose, cellulose acetate butyrate, PVP
WIP**	Polyvinyl acetate, ethyl-cellulose, crospovidone, crosscaramellose
pH-DP*** and WIP	Poly-acrylic acid, polycarbophil
pH-IP**** and WIP	Polyvinyl acetate cellulose ethers, cellulose ester,
Reverse enteric polymers	Methyl methacrylate, Eudragit E 100, Eudragit EPO, PVP, hydroxyl ethyl methacrylate
Enteric polymers	Aacrylic acid esters, Phthalate, hydroxyl phthalates
Spacing layer polymers	Ethyl cellulose, PVP

* Water insoluble polymers, ** Water insoluble polymers, *** pH-dependent polymers, **** pH-independent polymers

1.4 Ion-exchange resins

An ion exchange resin (inert organic compounds) is insoluble in saliva Ph. These compounds are long-chainhydrocarbons and exchange their ions in the solution or medium and form a drug-resin complex. These compounds are tasteless and release alimited amount of drug in the mouth. They may be cations exchange resin or anion change resin. Selection of the type of ion exchange resin used for the drug-resin complex is critical as they should be stable to prevent the breakdown of the drug-resin complex in the saliva and at the same time release the drug in the GIT [1].

Table 5

List of commonly used ion exchange resins [1]

Different types of resin	Commercial Name
Strong anion	Dowex 1, Duolite AP 143, Indion 454, AIR* 400
Weak anion	AIR 4B, Dowex 2
Strong cations	Purolite C 100 HMR, Indion 244, Dowex 50, Kyron –T-154, AIR 120
Strong cations	AIRP 69, Indion 254, Tulsion- T-344
Weak cations	Tulsion T 335, Tulsion 335, 339, Purolite C 102DR, AIRC 50, Doshion P544 (R), Indion 204-234, Kyron-T-104,
Weak cations	Indion 234, Kyron-T-134, AIRP 88, Tulsion T 339

* Amberlite IR,

1.4.1Reactions involved in Complexation of drug with resins [1]

- If drug is basic

$Re\text{-}COO^- H^+ + Drug^+ \rightarrow Re\text{-}COO\text{-}\ Drug^+ + H^+$

- If the Drug is acidic

$Re\text{-}N\ (CH_3)+ 3Cl^- + Drug\text{-} \rightarrow Re\text{-}N(CH_3)+ 3Drug\text{-} + Cl^-$

1.4.2Reactions involved in gastrointestinal fluids (Vummaneni 2012 et al)

Alkaline drug for:

Stomach

$Re\text{-}COO^- Drug^+ + HCl \rightarrow Re\text{-}COOH + Drug\text{-}\ HCl$

In intestine

$Re\text{-}COO^- Drug^+ + NaCl \rightarrow Re\text{-}COONa + Drug\text{-}HCl$

Acidic drug

In stomach

$Resin\text{-}NH_3Drug\text{-} + HCl \rightarrow Resin\text{-}NH_3Cl + DrugH$

In intestine

$Resin\text{-}NH_3Drug\text{-} + NaCl \rightarrow Resin\text{-}NH_3Cl^- + Drug(Sodium\ salt)$

1.5 Microencapsulation

It is a process of formation of thin coating around the active moiety (individual particles or droplets of liquid and materials) using compatible polymer to produce shell known as microcapsules. Polymer selection used in forming microcapsule is an important task [1, 5]

This method includes various techniques [1]

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

Of all these Coacervation phase separations,spray drying, air suspension coating aremostly used.

Polymers and ideal characteristics

- It should be unsolvable at salivary pH but readily soluble in pH 1.2
- It should not be discharged active agent in the mouth.

Coating polymer selection is a very crucial task based on the following factors:

Drug's particle size

- Flow properties of drug's particles
- Moisture sensitive
- Long-term stability
- Temperature
- Drug delivery technique

Table 6

Literature report on taste masking by micro-encapsulation [1, 6]

Name of drug	Drug formulation	Methods used
Acetaminophen	Dispersible tablet	WFBC*
Cimetidine / Caffeine	Chewable tablet	WFBC
Ciprofloxacin Fluor quinolone	Oily suspension, sachets	WFBC
Levofloxacin Fluor quinolone	Suspension	WFBC
Sildenafil citrate		TSFBC**
Chlor-pheniramine maleate Dextromethorphanhydrobromide	Mouth melt tablet	TSFBC
Acetaminophen	Chewable tablet	WFBC, TSFBC***
Theophylline	Dry suspension	TSFBC
Ampicillin trihydrate	Powders	Spray drying
Nizatidine	Sprinkles	Spray drying
Roxi-thromycin	Suspension	Spray drying
Clarithromycin	Powders	Spray congealing
Chloroquine di -phosphate	Powders	Coacervation phase separation
Metronidazole	Dry suspension	SE#
Aspirin, Ibuprofen, keto-profen and Fenamic acid		SE
Praziquantel		SE
Isoprothiolane		Spray drying
Indeloxazine HCl		Fluidized bed drying

* Wurster fluid bed-coating, ** Top spray fluid bed-coating, *** Tangential spray fluid bed coating, # Solvent evaporation

1.6 Granulation

It is a common methodof taste masking in process of tablet production .In this technique, insoluble binding agents are used so that bitter taste can be masked of drug. After taste-making granules can be formulated in the form of chewable and disintegrating tablets [1, 7]

Table 7

Literature report on taste masking by granulation [1, 8]

Name of drug	Pharmacological class	Granulating agent
Dextromethorphan	Anxiolytic	Cyclodextrin
Alprazolam	Anti-tussive	Eudragit E 100
Norfloxacin	Fluoroquinolone antibiotic	Meth acrylic acid ester
Macrolide antibiotic	Macrolides	Polycarbophil
Ondansetron	Antinausent, antiemetic	Polacrillin potassium
Ibuprofen	Anti-inflammatory	Micro Crystalline Cellulose
Calcium compounds	Mineral supplement	Sugar alcohol
Granisetron HCl	Anti-nausea, antiemetic	Glycerol behenate or glycerol

		palmate-stearate
Levofloxacin	Fluor quinolone antibiotic	Sugar alcohol, Castor oil
Clopidogrel sulphate	Antiplatelet	Sugar alcohol, Castor oil
Pristinamycin and Telithromycin	Macrolides	Glycerol stearate or beeswax
Vitamins	Diet supplement	Poly-glycerol ester of polyvalent fatty acids
Penicillin's, Macrolides	Antibiotics	Hydrogel or Wax
Erythromycin	Macrolide	Alginic acid

1.7Adsorption

A less soluble version of the drug can be done by forming a thin film of insoluble materials like silica gel and bentonite on the surface of bitter drugs, this process is called adsorption. The resultant material used in the formulation of the dosage form [1].

1.8 Pro-drug approach

The inactive form of the drug is known as a prodrug which undergoes biotransformation and releasesthe active moiety in the body. Hence, theaction of the drug is achieved. The geometry of drug is important in the sensation of taste which is altered in this process. Hereafter masking of the bitter drug is done this process is known as adsorption and resultant material obtained is called absorbents. Advantages of pro-drugs include: alteration in aqueous solubility, which enhance in lipophilicity, better absorption, change in membrane permeability and fewer side effects etc. Table 8 gives the list of active forms and their pro-drug methods done in last few years [9].

Table 8:

Example of taste masking by pro-drug approach [1]

Name of drug	Pharmacological class	Pro-drug approach
Erythromycin	Macrolide antibiotic	Alkyl ester
Lin-comycin	Lincosamide antibiotic	Alkyl ester, phosphate
Tetracycline	Broad spectrum antibiotic	3,4,5-trimethoxy benzoate salts
Clindamycin	Lincosamide antibiotic	Alkyl ester
Triamcinolone	Treat the skin disorders and ulcerative colitis	Diacetate ester
Chloramphenicol	Broad-spectrum Antibiotic	Palmitate or phosphate ester

1.9 Formulation of inclusion complexes

In this method, a complexing agentis used which have the ability to hide the bitterness of the drug by which decreasing its solubility on decreasing the number of drug particles which exposed to taste buds. The complexing agentis also called ligand and it acts as host in which foreign molecule may fit.Vander-walls forces responsible for the formation of an inclusion complex. Therefore inclusion complexes are ‘host-guest’ relationship [1, 10].

Table 9

Example of taste masking by inclusion Complexation [1]

Name of drug	Pharmacological class	Drug formulation	Agent used for Complexing
Zinc acetate dehydrate	Recover zinc deficiency		Saccharin, Anethol -β- cyclodextrin complex
Carbapentane citrate	Local anaesthetic	Oral liquid	Cyclo-dextrins
Dioscin	CVS disorders		βC*
Benexate hydrochloride		Antiulcer Granules	βC
Hexitidine	Anti-bacterial		βC
Zipeprol	Anti-tussive		βC
Guaiacol	Anti-diarrhetic		βC
Ibuprofen	NSAID	Solution	Hydroxypropyl βC
Gymnema sylvestre	Anti-diabetic	Oral liquid	βC, Chitosan
Metronidazole benzoate	Anti-bacterial		γC**
Levosulpiride	Anti-psychotic		βC
Chloroquine phosphate	Anti-malarial	Syrup	Tannic acid
Dimenhydrinate	Anti-emetic	Chewable tablet	Eudragit-S- 100

* β-cyclodextrin, ** γ-cyclodextrin

2. Evaluation of taste masking techniques

2.1 Evaluation of liquids and solids dosage forms

Multi-channel taste sensor was discovered by Soutakagi is called as E tongue. It consists of a different polymer with different characteristics. Information of taste transferred in the form of electrical signals to this polymers/lipid membrane. It is an instrument that measures and compares tastes. It carries out fast evaluation of oral formulations like chewable tablets, liquid, fast-dissolving tablets, lozenges and films etc [1, 10].

2.2 Panel testing

In this process group of around 5-10 volunteers asked the educated for taste evaluation by using reference solutions. Tastes measured by allocating numerical values to intensities of bitterness (e.g. 0-5) and sample solution are rated on this scales [9]

2.3 Evaluation of microspheres

Micro-particles spherical in shape obtained from protein or polymer are known as microspheres. In this process, thereleasing rate of the drug from microspheres is calculated this drug release rate can be used as the degree of taste masking attained [1].

2.4 Multi-channel taste sensor

It is used for In vitro evaluation. E-tongue is the automated sensing device which detects the magnitude of bitterness. Recognition, quantitative multicomponent assessment and artificial analysis of taste and flavour.

2.5Measurement of frog taste nerve response

In this process the adult bull frog was dissected tissue and cut it carefully than an electronic integrator are used to integrated and amplify nerve impulses. The peak height of integrated is than taken as magnitude response.

2.4 Spectrophotometry method

In this process take a known quantity of formulation in 10ml 0f distilled water in 10ml syringe by the revolving syringe end to end five times in 30seconds. And filter the medium through a membrane filter followed by spectrophotometric determination concentration of drug in filtrate. Then observed the concentration below the threshold concentration it can conclude that better taste can mask in the vivo methods. This parameter is applied for to evaluate mask granules of sparfloxacin with having threshold concentration 100microgram\ml.

4. Conclusion

The bitterness of oral pharmaceutical formulation is a major problem and influences patient compliance. Geriatrics as well as pediatrics trouble swallowing capsules and tablets, prefer liquid or sublingual/chewable solid dosage forms. Most of the oral dosage forms have an obnoxious taste. These methods do not only mask the taste of APIs but also heighten bioavailability, accessibility, and performances of dosage forms. Methods is used for addition of flavouring and, microencapsulation, sweetening agents, ion exchange resins, inclusion complexes, bitterness inhibitors, multiple emulsions granulation, adsorption and pro-drug approach.

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