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Review Article

Practical Approaches for Taste Masking of Bitter Drug: A Review

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ABSTRACT

Taste is most important organoleptic aspects about the acceptance of oral drugs. Bitter and unpalatable taste is a major problem of certain drugs in formulations. In market, there are numbers of pharmaceutical preparations available in which actives are bitter in taste. The improved palatability in these products has prompted the development of numerous formulations, which improved performance and acceptability. The bitterness of preparation also leads to patient incompliance. So masking of bitterness becomes essential and done by masking the bitter taste of drugs 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. Methods commonly used for taste masking involves various physical and chemical method that prevent the interaction of taste bud with drugs and are based on coatings, solid dispersion system and ion exchange resin, entrapment method and masking of taste buds etc. Taste masking of bitter drugs become necessity in case of oral administration and selection of technology depends upon the bitterness of drugs and their compatibility with taste masking agents that does not affect the bioavailability of drug

Keywords: *Taste buds, Flavors, Cyclodextrins, Eudragit, E-tongue*

Introduction:

Organoleptic properties are important considerations for development of a solid oral dosage form that can influence consumer preference and compliance. In the case of bitter drugs, taste is one of the most important parameter governing patient compliance[1] and oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers especially for pediatric and geriatric[2]. Chewing large pieces of gum or tablet is difficult for elderly patient and sometimes experiences the bitter or unpleasant taste of drug if the taste masking coatings rupture during mastication. Bitter sensation is the result of signal transduction from the receptor organs containing very sensitive nerve endings, which produce and transmit electrical impulses[3]. Masking the bitter taste of drugs 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.

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[4] (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[5].

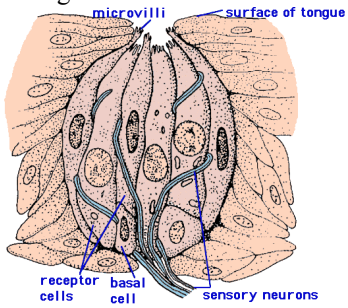

Fig. 1 Physiology of Taste Bud[4]

Four fundamental sensations of taste have been generally described- Sweet, Sour, Bitter, Salty and fifth widely accepted basic taste is Umami[6]. These tastes consistently stimulate taste bud in specific parts of the tongue as sweet and salty mainly at the tip, sour at sides, bitter at back (Fig. 2).

Fig. 2 Taste Points in Tongue[7]

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Taste Signaling Pathways

Taste transduction begins with the interaction of a tastant (eg. medicine or food) with taste receptor cells in the taste buds[8] (Fig 3). The tastant binds with G-Protein coupled receptors (GPCRS) in the cells triggering the release the release of G-Protein called Gustducin.

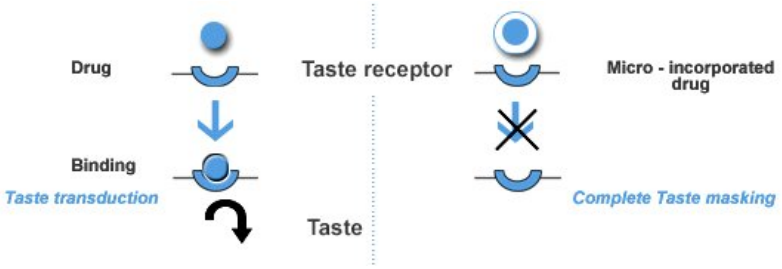

Fig. 3 Taste Signaling Pathways[8]

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 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 extra cellular 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[9] (fig. 4).

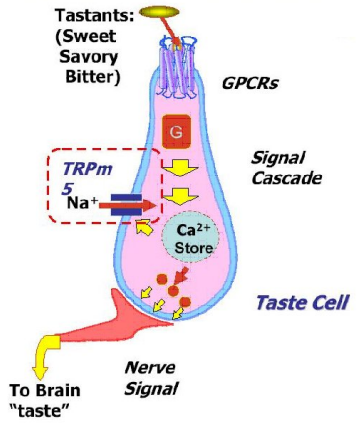

Fig. 4 Taste Blocking Mechanism[10]

Taste Masking Technologies

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. The first includes reduction of drug solubility in saliva, where a balance between reduced solubility and bioavailability must be achieved. Another approach is to alter the ability of the drug to interact with taste receptor[11]. Popular approaches in the development of taste masking in liquid dosage form include use of flavor followed by viscosity modification and if failed, by ion exchange resin (Fig. 5). In case of solid dosage form, chemical modification (Prodrugs and salt formation), Host Guest locking, solid dispersion method effectively masked the unpleasant taste. Drug particle coating technique successfully masks the taste in all type of formulation.

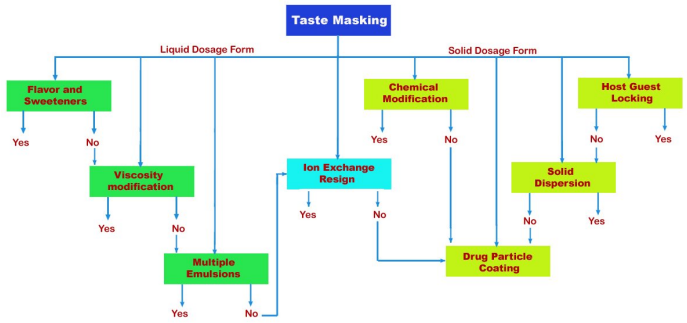

Fig. 5 Taste Masking Technologies uses in liquid and solid dosage forms

1. Flavor Modification and Sweeteners

Using flavors from natural or synthetic sources, being simplest approach for taste masking, unpleasant taste of drugs modified[12] (table-1). Flavors and sweeteners overwhelm the unpleasant taste by occupying the taste buds and thus suppressing the taste of drug. Traditionally, Slight bitter and sour taste of drugs are effectively masked by the citrus fruits, however, this method fails in case of highly bitter drugs and used to improve the palatability of formulations

Table-1: Commonly used natural flavoring agents for taste masking

Taste	*Masking agents*
Bitter	Lemon, Orange, Cheery, Grapefruit, Raspberry, Lime, Coffee, Chocolate
Sour	Lemon, Lime, Orange, Cherry, Grapefruit
Salty	Berries, Mints, Fennel, Anise, Grape

Flavors and sweeteners chosen based on their specific taste and release profiles e.g. Sweeteners like sodium saccharin, acesulfame potassium (aspartame) give instant sweetness, whereas sweeteners like monoammonium glycyrrhizate give lingering sweetness and used either alone or in combination.

2. Viscosity Modification

Enhancement of viscosity in liquid formulations by thickening agents such as natural gums or carbohydrates can mask the unpleasant taste of drug by formulating a covering layer on the tongue and act as barrier between drug particles and taste buds, thus lowering the diffusion of drug from saliva into the taste buds[13]. For viscosity enhancement in liquid formulations, polyethylene glycols and carboxy methylcellulose are induced which not only increases the stability of liquid formulation but surprisingly, provides taste masking of unpleasant tasting medicines. For examples, in cough syrups, terbutaline given in doses of 4mg/5ml can be effectively administered by increasing the viscosity of the formulation.

3. ***Host Guest Locking Method***

In host guest locking method, host molecule has a cavity in which the guest drug occupies and the taste of the guest drug masked by two approaches[14] as

a. By decreasing its oral solubility on ingestion and

b. By decreasing the amount of drug particles exposed to taste buds, reducing the perception of bitter taste.

Cyclodextrins are widely used in industry due to their ability to form inclusion complexes with a variety of molecules. Cyclodextrins are cyclic oligosaccharides composed of 6, 7, 8 glucose molecules (alpha-beta or gamma respectively) having supramolecular structures that involve intramolecular interactions[15].

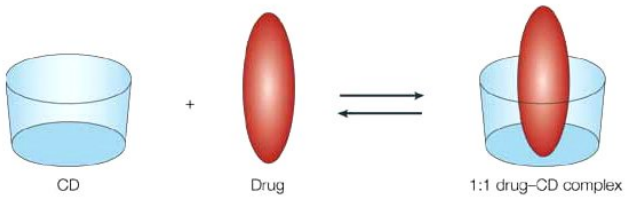

Fig. 6: Cyclodextrin Drug complex in 1:1 ratio[16]

Bitterness elimination is depend upon the extent of Complexation of guest molecule with host, value of complex association constant, temperature and the host / guest ratio (Fig 6 & 7)

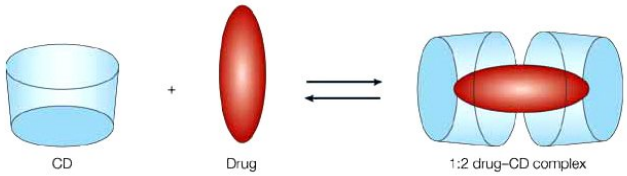

Fig. 7: Cyclodextrin Drug complex in 1:2 ratios[16]

For bitter drug forming a 1:1 complex with cyclodextrins, more than 99% of the bitter drug is complexed with cyclodextrins and as complexed molecule cannot react with the taste bud in the buccal cavity, no bitter taste perceived[17] and suppression of bitter taste by cyclodextrin was increase in increasing order of alpha, gamma, and beta cyclodextrin[18].

4. Drug Particle coating

Involves the covering total surface of particle with enough coating so that the taste is not apparent to the users and mask the bitter taste of drug. Any nontoxic polymer that is insoluble at pH 6.2 and soluble at acidic pH would be acceptable to coat the bitter drugs and should be inert in nature.

Methods used for polymer coating are

a. Fluidized Bed / Spray Coating[19]: In fluidized bed coating, powders as fine as fifty micrometer fluidized in an expansion chamber by means of heated, high velocity air and the drug particles coated with a coating solution as a spray through the nozzle (Fig 6).

b. Microencapsulation: is a process of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions. Different methods used for Microencapsulation are air suspension, coacervation phase separation, solvent evaporation, spray drying and congealing, pan coating technique[20] (table-2). In practice Microencapsulation by spray drying[21] is conducted by dispersing a core material in coating solution in which the coating solution is dissolved and then by atomizing the mixture into an air stream[14].

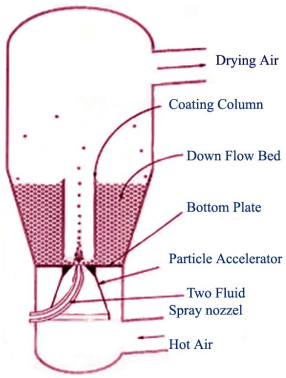

Fig. 6: Fluidized Bed / Spray Coating technique[19]

Spray drying is an effective method of taste masking because this method is cost effective and requires no solvent and it can produce a more dense film than other methods without moving material for drying[22].

c. Extrusion coating: technology involves softening of active blend using the solvent mixture of water soluble PEG, menthol and expulsion of softened mass through the extruder or syringe to get a cylindrical product and these cylindrical shaped products used to coat granules of bitter taste drugs and masks the taste[23].

Table-2: Marketed taste masked drugs by drug particle coating technique

TECHNIQUE	*POLYMER*	*TASTE MASKED DRUGS*
Air Suspension Coating	Methacrylic acid copolymer	Ibuprofen[24]
Phase separation Coacervation	Eudragit E-100, Chitosan	Clarithromycin[25], Paracetamol
Fluidized Bed / Spray Coating	Hydrogenated Oil and Surfactant	Indeloxazine[26]
Solvent Evaporation Method	Eudrgit E, PEG, Ethyl Cellulose	Pseudoephedrine[27] Ranitidine[28]
Extrusion Coating	Eudragit E-100	Oxybutinin[29], ofloxacin[30], pirezepin[31]

5. Taste Masking by Ion Exchange Resins

Based on Complexation of drugs with ion exchange resins. Ion exchange resins are water insoluble, cross linked high molecular weight polyelectrolytes[32] containing salt forming groups in repeating position on the polymer chain which exchange their mobile ion of equal charge with the drug molecule[33]. As taste perception of bitter drugs is experienced in the mouth at taste buds, complexed drugs resinate does not release drug in mouth due of scarcity of exchangeable ions (at pH 6.7) in the saliva and when complex comes in contact with GIT fluids (at acidic pH), complex is broken down quickly and drug is release[34]. Resins being polyelectrolyte have extensive binding sites leading to very high drug loading ability[35,36]. Ion exchange resins have received considerable attention because of their versatile properties as drug delivery vehicles, chemically

inert and free from local and systematic side effects[37,38] possess long-term safety even while ingesting large doses and also compatible with all conventional solid, semisolid

Table-3: Commonly used ion exchange resins[41]

Type	Functional Group	Matrix Structure	Commercial Resins	Taste masked drugs
Weak cation	-COOH	Methacrylic acid Divinylbenzene	Indion 204, Tulsion T-335, Amberlite IRC 50	Norfloxacin, Ofloxacin, Roxithromycin
	$-COO-K^+$	Methacrylic acid Divinylbenzene	Tulsion T-339 Indion 234, Amberlite IRP 88	Ciprofloxacin, Chloroquine
Strong cation	$-SO_3H$	Polystyrene Divinylbenzene	Indion 244, Dowex 50, Amberlite IR 120	Chlorpheneramine maleate, Ephedrine Hydrochloride
	$-SO_3Na$	Sodium polystyrene Divinylbenzene	Tulsion T-344, Amberlite IRP 69 Indion 254	Dicyclomin, Dextromethorphen, Pseudoephedrine, Buflomedil, Rantidine
Weak anion	$N-R_2$	Polystyrene Divinylbenzene	Amberlite IR4B, Dowex 2	NTM
Strong anion	$N-R_3$	Polystyrene Divinylbenzene	Amberlite IR400, Dowex 1, Indion 454, Duolite AP143	NTM

NTM - not used in taste masking

and liquid dosage forms[39]. Ion exchange resin classified in four major groups, strong acid cation exchange resin, weak acid cation exchange resin, strong base anion exchange resin, weak base anion exchange resin[34]. Majority of oral preparation containing bitter drugs use cation exchange resins for taste masking[40] (table-3). Bitter cationic drugs get absorbed on to weak cationic exchange resins of carboxylic acid functionally to form the complex, which is non bitter.

To bind the drug with resin, the drug repeatedly exposed with resin for prolonged contact and drug attached to the oppositely charged resin through weak ionic bond, so the dissociation of the drug-resin complex dose not occurs under salivary pH conditions, which suitably masks the unpleasant taste of drug. Strong acid cation exchange resins used for masking the taste of basic drug functions through out the entire pH range whereas weak acid cation exchange resin functions at pH more then six. Strong base cation exchange resin function through out the entire pH range[42].

6. Solid Dispersion

Dispersion of one or more active ingredients in an inert carrier or matrix in solid state is utilizes in solid dispersion for masking the bitter drugs[43] and approaches used are melting method, solvent method and melting solvent method. Chiou and Riegelman[44] defined solid dispersion as "a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixture". In melting method, drug and solid carrier melted together, cooled and solidified whereas in solvent method, taste masking done by dissolving the drug and carrier in common solvent followed by evaporation. For example, taste masking of artemether[45] (ether derivative of artemisinin, a well known antimalarial drug) carried by solid dispersion technique using monoammonium glycyrrhyzinate pentahydrate.

7. Multiple Emulsions

Multiple emulsions are complex poly dispersed systems having oil in water and water in oil emulsion simultaneously existence, stabilized by lipophillic and hydrophilic surfactants respectively[46], prepared by dissolution of drug in inner aqueous phase of w/o/w emulsion under good shelf stability condition[47]. This technique successfully utilizes in masking the bitter taste of chloroquine[48] (broad-spectrum antimalarial drug).

8. Chemical Modification

a) **Formation of salt or derivatives:** Decreasing the solubility of drug by its salt formation makes the drug as tasteless as become less soluble in saliva so less sensitive to taste buds. For example Penicillin modified as N, N- di benzyl ethylenediamine diacetate salts or N, N bis (deyhdroabiety) ethylene diamine salts is tasteless.

b) **Prodrug formation:** Prodrug, a chemically modified inert drug precursors, which upon biotransformation converts into pharmacologically active parent compound shows its activity (table-4).

Table-4: Examples of Prodrugs with improved taste

Parent Drug	Prodrug
Erythromycin[49]	Erythromycin Propionate
Clindamycin[11]	Clindamycin palmitate ester
Chloramphenicol[11]	Chloramphenicol palmitate ester
Morphine	N-oxide derivatives of all Morphine
Triamcinolone[11]	Triamcinolone diacetate ester
Gabapentin[50]	Gabapentin XP13512
Norfloxacin[50]	Norfloxacin alkyl carbamates

9. Desensitizing agents[9]

Desensitizing agents like phenols, sodium phenolates desensitize the taste buds by interfering with taste transduction (Fig. 4), the process by which taste message from the mouth to the brain and thus mask the taste of drug.

10. Use of lipoproteins

Lipoprotein composed of lipids (phosphatidic acid) and protein (β lactoglobulin) reduces the bitter taste of drugs most effectively by suppressing bitter taste[51]. Basic and

hydrophobic drugs such as quinine, papaverine, denatortium, caffeine and L-Leucine and propranolol, theophylline are very bitter in taste and their taste is effectively suppressed by phosphatidic acid- lactoglobulin due to binding to the hydrophobic region of the receptor membranes leading to suppression of the responses to the bitter substances.

11. Use of amino acids

Amino acids and their salts (alanine, taurine, glutamic acid, glycine) in combination with bitter drugs reduces the bitterness of the drugs for example, 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[52].

EVALUATION

Evaluation of taste masking is tedious work as the taste sensation varies person to person and involves taste masking efficiency as quality control parameter and determining the rate of release of drug from taste-masked complex and asses by *in vivo* and *in vitro*.

In vivo Evaluation[53]

In vivo taste evaluation carried out on a trained taste panel of healthy volunteers with organoleptic sense, with their prior consent. On placing the dosage form in mouth for 60 seconds, bitterness recorded against pure drug using a numerical scale. The numerical scale may bears values as 0 = pleasant, 1 = Tasteless, 2 = No bitter but after taste give bitterness, 3= immediately gives bitterness, 4 = slightly bitter, 5 = extremely bitter.

In vivo assessment usually demands large panels and elaborate analysis, raises safety and scheduling issues and can be time consuming and expensive.

In vitro Evaluation

Invention of "E-Tongue" electronic sensor array technology overcomes this problem, which is a device for recognition, quantitative multicomponent analysis and artificial assessment of taste and flavor. It recognizes three levels of biological taste including receptor level (Taste buds in humans, probe membranes in E-Tongue), circuit level (neural transmission in humans, transducer in E-Tongue), and perceptual level (cognition in the thalamus humans, computer and statistical analysis in the E-Tongue)[54,55]. The probes consist of a silicon transistor with proprietary organic coatings, which govern the probe's sensitivity and selectivity, and measurement done potentiometrically. Each probe is cross selective to allow coverage of full taste profile and statistical software interprets the sensor data into taste patterns[56]. Liquid samples directly analyzed without any preparation, whereas solids require a preliminary dissolution before measurement. Reference electrode and sensors are dipped in a beaker containing a test solution for 120 seconds (fig. 7). A potentiometric difference between each sensor and a reference electrode measured and analyzed by the E-Tongue software. Sensory analysis employs to measure and control taste and flavor quality during manufacturing process development, clinical use, stability studies, validation, commercial manufacturing and batch release[57] (table-5).

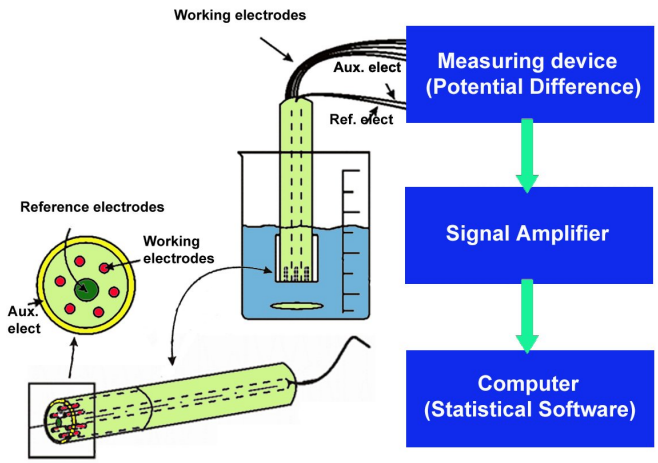

Fig. 7: Evaluation of taste using e-tongue[55]

These data represent the input for mathematical treatment that will deliver results. The E-Tongue enables us to test taste accurately without the need for human volunteers at earlier stages of drug development. Furthermore, the E-Tongue cannot be poisoned and it won't fatigue or lose its sense of taste after long periods of testing.

Table-5: Sensory analysis using e-tongue

Methods	*Types*	*Description*	*Primary use*
Affective tests	Paired preferences	Measures the response of product with paired reference	Quality control
	Acceptance	Measures the degree ranging from "like extremely" to "dislike extremely"	Frequently used by market research and R & D
	Specificity	Determines the appropriateness of a specific attribute	-
Descriptive methods	Flavour profile	Objective description of product (characteristics and intensities)	In food and Pharma product and process development, quality assurance
Discrimination	Difference	Differentiates between samples for specific characteristic	Quality control, Cost control
	Ranking test	Rank for specific characteristic	Preliminary screening
Scaling tests	Scoring	collect information on specific product attributes	Used in meat and dairy industries for quality

CONCLUSION

Taste masking of bitter drugs become necessity in case of oral administration and lot of technologies available that effectively mask the objectionable taste of drug but require skillful application, which can improve product preference largely and selection of technology depends upon

the bitterness of drugs and their compatibility with taste masking agents that does not affect the bioavailability of drug. Extensive work had been carried out till date in order to taste masking of bitter drugs and their evaluation. Despite the effect that a lot of dosage forms available in the market, still a lot of work needs to be done to standardize the techniques.

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