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REVIEW ON TASTE ABATEMENT TECHNIQUES

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ABSTRACT

An organoleptic property like taste, odour and mouth feel etc. forms the major concerning factors that distinguish different products and improves their palatability problem. The problem of bitter taste of drug in paediatric formulations is a challenge to the formulators in the present scenario. Taste masking of obnoxious drugs has gained the importance as the most of them are administered orally. This reason is an initiative for the development of various taste masking technologies by which the characteristics of the dosage form is improved and good patient compliance is achieved. This paper reviews different methods are available to mask undesirable taste of the drugs, with the applications. It includes flavours, sweeteners and amino acids, polymer coating, ion exchange resins, chemical modification, formation of salt or derivatives , prod rug approach, spray congealing with lipids, inclusion complexes, granulation, solid dispersion, adsorption, liposomes, pH modifiers, multiple emulsions, miscellaneous: by effervescent agent ,rheological modification ,continuous multipurpose melt technology.

INTRODUCTION

Taste is important parameter in administering drugs orally. Taste is ability to detect the flavour of substance like food, drugs etc. Objectionable taste is one of the most important formulation problems that are found in certain drugs. In earlier days it was believed that the drugs having bitter taste are more efficient as well as more curable. This concept has been reversed with development of numerous formulation techniques. The oral administration of bitter drug is major concern for patient compliance. Administration of unpalatable drugs is hampered by their unpleasant taste particularly in case of paediatric, geriatrics, bed ridden and Non-co-operative patient.[1] Taste can be separated into five primary taste qualities sweet, sour, salty, bitter and umami or savory. Within hours of after birth, infants reject bitter taste and prefer sweet and umami taste.[2]

1.1. Taste- Salty taste (edge, upper portion)

The salty taste is one among the four taste receptors of tongue. They are located on the edge and upper front portion of the tongue. The cations of the salts especially sodium cations are mainly responsible for salty taste and anions also contribute to a lesser extent.

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. Sweet taste is not caused by any single class of chemicals.

Sour taste (along sides in back)

The sour taste is also one of the four taste receptors of the tongue. They occur at sides 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 toward the back of the tongue. It is stimulated by a variety of chemical substances, most of which are organic compounds, long chain compounds, alkaloids, although some inorganic compounds such as magnesium and calcium also produce bitter sensations. [3,4,5]

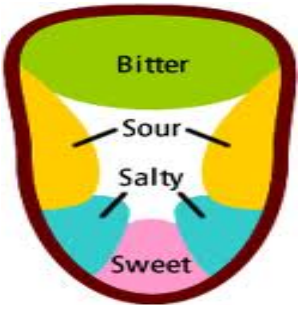


Fig. 1 Taste Points in Tongue

1.2. Anatomy of Tongue

Two types of special structures are seen on tongue,the papillae and taste buds. The taste buds are sense organ of taste. Human have around 10,000 taste buds which appers in fetus at about three months. A single taste bud contains 50-100 taste cells.[6]

1.3. Distribution

Taste buds are also present on palate, pharynx, epiglottis and larynx. Tongue consists of numerous structures called papillae. There exists different types of papillae, of which fungiform papillae contain single taste bud on the tip and circumvallate papillae contains several taste buds. However, filiform papillae donot contain taste buds even their number is more[7,8,9].

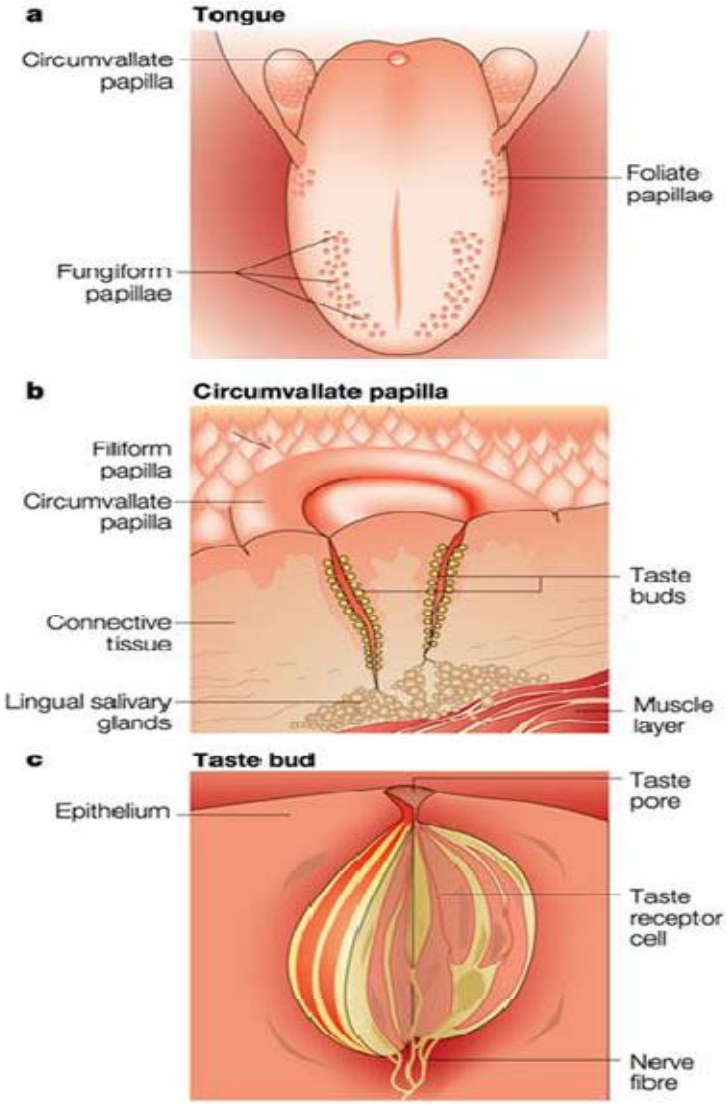


Fig. 2: Structure of taste bud

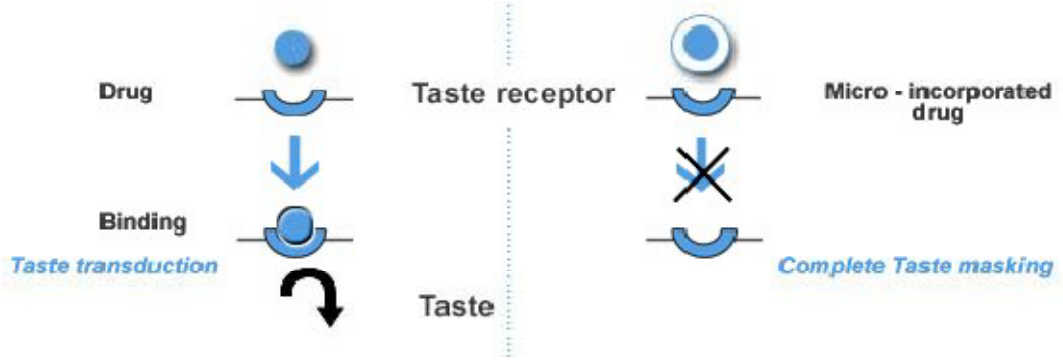
1.4. Physiology of taste-

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.

1.5. Taste Signaling Pathways

Taste transduction begins with the interaction of a tastant (eg. medicine or food) with taste receptor cells in the taste buds8 (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



The process of taste sensation begins whenGustducin 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.[10]

AN IDEAL TASTE MASKING PROCESS AND FORMULATION SHOULD HAVE THE FOLLOWING PROPERTIES.

1) Involve least number of equipments and processing steps.

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

3) No adverse effect on drug bioavailability.

4) Require excipients that are economical and easily available.

5) Least manufacturing cost.

6) Can be carried out at room temperature.

7) Require excipients that have high margin of safety.

8) Rapid and easy to prepare. [11]

TASTE MASKING TECHNIQUE

3.1. Taste masking with ingredients such as **flavours, sweeteners and amino acids**: This is the simplest and commonest approach used for taste masking.

3.2**. Polymer coating:** Coating provides a physical barrier to the drug particles which minimizes interaction between drug and taste buds.

3.3. **Ion exchange resins**: Ion exchange resins provide taste masking by complex formation.

3.4. **Chemical Modification**

a) Formation of salt or derivatives:

b)Prodrug approach: it is a chemically modified inert drug precursor.

3.5. **Spray congealing with lipids**: Lipids and lipophilic vehicles are used to provide taste masking property.

3.6. Formation of **inclusion complexes** with cyclodextrins: The drug molecule fits into the cavity of complexing agent forming a stable complex.

3.7. **Granulation:**

3.8. **Solid dispersion:** Solid dispersions using insoluble matrices or bland matrices may be used to mask the bitter taste of drugs

3.9. Taste masking by **adsorption** involves adsorb the drug, removing the solvent,and dried adsorbates in the preparation of the final dosage form.

3.10. Development of **liposomes:** liposomes are vesicular structures consisting of hydrated baitlayers which form spontaneously when phospholipids are dispersed in water.

3.11**. pH** modifiers

3.12. **Multiple emulsions**: By providing entrapment of bitter component into the emulsion, taste masking can be achieved.

3.13**. Miscellaneous**:

- By effervescent agent
- Rheological modification
- Continuous multipurpose melt technology
- Freeze drying process[12,13]

3.1. Taste masking with flavors, sweeteners, and amino acids

This technique is the most simple and very old technique for improving taste characteristics of active component of the formulations. Taste masking can be achieved by using various amino acids like glycine, alanine, leucine etc. Materials available for taste masking can be classified according to basic taste that is to be masked. [14]

Sweet	Vanilla, Bubble gum, Grapefruit
Acid	Lemon, Lime, Orange, Cherry, Grapefruit
Metallic	Grape, Marsh, Mellow, Gurana, Berries, Mints
Bitter	Liquorices, Coffee, Chocolate, Mint, Grapefruit, Cherry, Peach, Raspberry, Orange, Lemon, Lime.

Table 1: Basic Taste Masking Agents

A survey of the taste preferences of human race, as a whole, indicates that sweet taste is very aggreeable 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 artificials and natural sweeteners used in pharmaceutical products, their relative sweetness levels, and pertinent comments.

Sweetening agents	Relative sweeteness*	Comment
Aspartame	200	Not very stable in solution
Acesulfame potassium	137-200	Bitter after taste if used in higher concentration
Cyclamate	40	Banned
Glycerrhizin	50	Moderately expensive
Lactose	0.16	Large amount required
Manitol	0.60	Negative heat of solution
Saccharin	450	Unpleasent after taste
Sucrose	1	Most commonly used
Sucralose	600	Synergestic sweetening effect
*Sucrose is taken as a standard of 1 for comparison		

Table 2: Relative sweeteness of commonly used sweeteners

Flavors and sweeteners overwhelm the unpleasant taste by occupying the taste buds and thus suppressing the taste of drug. Flavors and sweeteners are chosen based on their specific taste and release profiles. Flavors are always a combination of various components that are formulated together to give a desired flavor profile. These components include base flavors, coolants, and desensitizers. The selection of flavouring agent should be complementary with sweetening agent and colouring agent in order to improve the aesthetics parameters to the formulations.[15.]

Flavoring agents can be natural or synthetic in nature. Natural flavors are as Peppermint, Lemon oil; Clove, Balsam, funnel and other distilled fractions. These are available as concentrated extracts, alcoholic or aqueous solutions, syrups or spirit. Selection of suitable flavouring agent to be added depends on the original sensation of drug substance. The cooling effect of some flavours aids in reducing after-taste perception. Eucalyptus oil is a major constituent of many mouth washes and cough syrup formulations.[16] Sweeteners are commonly used in taste masking of drugs. These are commonly used in combination with other taste masking technologies. These can be mixed with bitter drugs so as to improve the taste of the core material. Sweeteners are classified into natural and synthetic, based on the origin. These sweeteners are used in combination with sugar alcohols like citric acid) to increase the taste masking efficiency of the sweetener. Each sweetener will have their own significance in taste masking and different value of sweetness when compared to standard (Sucrose), There is often a correlation between the chemical structure of a compound and its taste.[16]

This technique is the foremost and the simplest approach for taste masking, especially in the case of pediatric formulations, chewable tablets, and liquid formulations. But this approach is not very successful for highly bitter and highly water soluble drugs. [17]

3. 2. Polymer coating of drug-

In some instances, sweeteners and flavors may not be sufficient to mask bitter drugs, so alternative methods of taste masking need to be employed.[18] Polymer coating is an excellent method of taste masking of bitter drugs. It avoids the direct contact of bitter drugs on taste buds. The coating acts as a physical barrier to the drug particles, thereby minimizing interaction between the drug and taste buds. Any nontoxic polymer that is insoluble at pH 7.4 and soluble at acidic pH, would be an acceptable alternative for taste masking. Coating of chewable tablets provides excellent taste masking while still providing acceptable bioavailability. [19] The selection of polymer is based on it physicochemical property and its compatibility with drug .Choosing

one of the polymers is not a simple selection. Before making the decision on coating material, the following factors of drug are to be considered

- Particle size
- Flow properties
- Moisture sensitivity
- Long term stability
- Effect of temperature on processing
- Form of Drug delivery etc.[20]

Water Soluble Polymers**:**

Cellulose acetate, cellulose butyrate, polyv inylpyrol li done, hydroxyethyl cellulose etc.

Water Insoluble Polymers*:*

Cellulose ether, cellulose esters, polyvinyl acetate etc. [21,22]

It is classified based on the type of coating material, coating solvent system, and the number of coating layers.

Methods used for polymer coating are

a. Fluidized Bed / Spray Coating**:** 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.

b. Extrusion coating (Dispersion 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.

c. Microencapsulation**:** is a process of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions. This is nanotechnology based technique. Different methods used for Microencapsulation are air suspension, coacervation phase separation, solvent evaporation, spray drying and congealing, pan coating technique, interfacial polymerisation.[23,24,25]

Air Suspension Coating	Methacrylic acid copolymer	Ibuprofen

Phase separation Coacervation	Eudragit E-100, Chitosan	Clarithromycin,Paracetamol
Fluidized Bed / Spray Coating	Hydrogenated Oil and Surfactant	Indeloxazine
Solvent Evaporation Method	Eudrgit E, PEG, Ethyl Cellulose	Pseudoephedrine,Ranitidine
Extrusion Coating	Eudragit E- 100	Oxybutinin, ofloxacin, pirezepin

Table-3: Marketed taste masked drugs by drug particle coating technique

Coating agents employed includes gelatin, povidone, hydroxy propyl methylcellulose, ethyl cellulose, bees wax, carnauba wax, acrylics and shellac. In practice Microencapsulation by spray drying 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.

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.

3.3. Taste masking using inclusion complex

This is the one of the latest and current technique for the taste masking with beneficial advantage of enhanced solubility of poorly soluble and low dose drugs. In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent, i.e. the host molecule, forming a stable complex or physical forces such as van der Waal's forces and hydrophobic interactions stabilize the complex that is formed. Cyclodextrin (CD) is the most widely used complexing agent. Cyclodextrins are a sweet, nontoxic, cyclic oligosaccharides obtained from starch, which have the ability to form host/guest inclusion complex both in solution and in solid phase. Molecules or functional groups that cause unpleasant taste can be hidden from the sensory receptors by encapsulating them within the cyclodextrin cavity. These complex molecules are strongly hydrated on the outer surface thus they do not get attached to the taste bud. Various types of

cyclodextrins are used for complexation according to the property of drug eg. Beta cyclodextrin, gama CD, hydroxypropyl βCD, methyl βCD etc.

Each CD differs in its ring size andsolubility. Of the 3 naturally occurring CD, the cavity size of α-CD is insufficient formany drugs and γ-CD is expensive. β-CD has been widely used in the early stages of pharmaceutical applications because of its ready availability and cavity size suitable for the widest range of drugs. β -cyclodextrin is the most widely used complexing agent for inclusion type complexes.[26,27,28]

Method of preparation of inclusion complex includes the following methods-

Co-grinding, kneading, solid dispersion, solvent evaporation, co-precipitation, spray drying and freeze drying. The effectiveness of a method depends on the nature of the drug and CD.

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 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

Factors influencing inclusion complex formation –

Three factors are mainly responsible i.e. charge and temperature.

Charge -Complex formation is better when the CD and the drug carry opposite charge but may decrease when they carry the same charge. For many acidic drugs forming anions, the cationic (2-hydroxy-3 [trimethylammonio] propyl)-β- CD acted as an excellent solubilizer.

In the case of ionisable drugs, the presence of charge may play a significant role in drug/CD complexation and hence a change in the solution pH can vary the complex constant.

Temperature- Temperature changes can affect drug/CD complexation. In most cases, increasing the temperature decreased the magnitude of the apparent stability constant of the drug/CD complex and it might be result of possible reduction of drug/CD interaction forces, such as Van derWaals and hydrophobic forces with rise of temperature. However, temperature changes may have negligible effect when the drug/CD interaction is predominantly entropy driven (i.e, resulting from the liberation of water molecules hydrated around the charges of guest and host molecules through inclusion complexation).[29,30]

Advantages of Cyclodextrin Inclusion Complexation

CDs have mainly been used as complexing agents to increase the aqueous solubility of poorly water-soluble drugs and to increase their bioavailability and stability. In addition, CDs have been used to reduce or prevent gastrointestinal or ocular irritation, reduce or eliminate unpleasant smells or tastes, prevent drug-drug or drug-additive interactions, or even to convert oils and liquid drugs into microcrystalline or amorphous powders.[31]

3.4. Ion exchange resins

Ion exchange resins are synthetic organic polymers inert in nature, consists of a hydrocarbon chain to which insoluble groups are attached and they have ability to exchange their labile ions for ions present in the solution with which they are in contact. [32]

Physical properties of Ion exchange resin

The ion exchange resin behave as hygroscopic gel, swelling or shrinking reversibly with desorption or absorption of moisture or water.

1. Cross linking: It affects many properties like swelling and strength of ion exchange resin like as it increase, swelling decrease.

2. Swelling*:* In polar solvents swelling occurs while in non polar solvents contraction occurs. The degree of swelling is also affected by the electrolyte concentration.

3. Particle size and porosity: Large surface area and small particle size will increase the rate of ion exchange.

4. Regeneration: The ion exchange resins after use get deactivated and can be regenerated by treatment with aqueous acid followed by washing with water for cation exchanger and with sodium hydroxide for anion exchanger. [33] Ion exchange resins are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium. The most frequently employed polymeric network used is a copolymer of styrene and divinylbenzene (DVB). Apart from thisother polymers such as those of acrylic and methacrylic acid cross linked with DVB and containing appropriate functional groups, have been used as ion exchange drug carriers. Synthetic ion exchange resin has been used in pharmacy and medicine for taste masking or controlled release of drug as early as.

Types-

Based on the charge of the functional groups present, ion exchange resins are classified into cation exchange resins and anion exchange resins. With in each category, they are classified into strong and weak depending on their affinity for counter ions. Cation exchange resins are

exchangers of sodium, potassium or aluminium salts and anionic resins are for chloride ions. The drugs are loaded on to the resins by column method and batch method.

Column method:

Highly concentrated drug solution is passed through the column containing resins. Maximum efficiency is best obtained by the column method.

Batch method:

In this method the drug solution is agitated with a quantity of resin until equilibrium is attained.[34,35]

Type	Functional group	Polymer Backbone	Commercial resins
Strong anion	-N+R3	Polystyrene -DVB	Amberlite IR 400,Dowex 1
Weak anion	-N+R2	Polystyrene - DVB	Amberlite IR 4B, Dowex2
Strong cation	-SO3H	Polystyrene - DVB	Amberlite IR 120,Dowex 50
Weak cation acid	-COOH	Methacrylic -DVB	Amberlite IRC 50, Indion 204,234, Tulsion 335,339

Table 4: Common ion exchange resins

Reactions involved in complexation of drug with resins

Acidic drug

Re-N(CH3)+ 3 Cl- + Drug- →Re-N(CH3)+ 3 Drug- + Cl-

Basic drug

Re-COO-H+ + Drug+ R→e-COO- Drug++ H+

Typical reactions involved in gastrointestinal fluids

Acidic Drug

In stomach

Re-N (CH3)+ 3 Drug- + HCl R→e-N(CH3) 3 Cl + Drug (Free form)

In intestine

Re-N (CH3)+ 3 Drug- + NaCl R→e-N(CH3)+ 3 Cl- + Drug (Sodium salt)

Basic Drug

In stomach

Re-COO- Drug+ + HCl →Re-COOH +Drug- HCl

In intestine

Re-COO- Drug+ + NaCl →Re-COONa+ Drug-HCl

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.[36,37]

4.5. Solid dispersion system:

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. Chiou and Riegelman defined solid dispersion as "a dispersion involving the formation of mixtures of drugs with water soluble carriers by melting of their physical mixture". A carrier used in solid dispersion system includes Povidone, Polyethylene Glycol of various molecular weights, Hydroxy Propyl Methyl Cellulose, Urea, Mannitol and Ethyl Cellulose. [38]

Various approaches for preparation of solid dispersion are described below:

1. Melting method

It was first proposed by Sekiguchi and Obi in 1961, to prepare fast release solid dispersion dosage forms. The physical mixture of a drug and water soluble carrier was heated until it melted. The melted was then cooled and solidified rapidly in an ice bath with vigorous stirring. The final solid mass was crushed, pulverized and sieved. Such a technique was subsequently employed with some modification by Goldberg et al and Chiou with Riegelman. To facilitate faster solidification, the homogenous melt was poured in the form of a thin layer onto stainless steel plate and cooled by flowing air or water on the opposite side of the plate. Some systems such as griseoulvin and citric acid were found to harden more rapidly if kept at 37 deg Celsius or higher temperatures.

2. Solvent method:

It has been used for a long time in the preparation of solid solutions or mixed crystals of organic or inorganic compounds. They are prepared by dissolving a physical mixture of two solid components in a common solvent, followed by evaporation of the solvent. The method was used to prepare solid dispersions of beta-carotene polyvinyl pyrrolidine, griseofulvin-polyvinylpyrrolidine, sulphathaizole-pvp-steroid-pvp, reserpine-pvp, reserpine-deoxycholic acid.

3. Melting solvent method:

It was shown 5-10% w/w of liquid compounds could be incorporated into polyethylene glycol 6000 without significant loss of its solid property. Hence its first possible to prepare solid dispersions by first dissolving a drug in a suitable liquid solvent and then incorporating the solution directly into a melt of polyethylene glycol, without removing liquid solvent.

4. Hot melt extrusion

Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. When compared to melting in a vessel, the product stability and dissolution are similar, but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. Solubility parameters are investigated to predict the solid state miscibility and to select matrices suitable for melt extrusion. High shear forces resulting in high local temperatures in the extruder be a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding. Though well documented and researched, this technique is not popular commercially because of difficulties with scalability at the industrial level.[39,40,41]

4. 6. 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.[42]

b] Prodrugs

The term "Prodrug" was first introduced by Albert in 1958.It is a chemically modified inert drug precursor, these are therapeutic agents that are initially inactive but on biotransformation liberate active metabolite by which the therapeutic efficacy is obtained. Prodrugs are synthetic derivatives (e.g. esters and amide) of drug molecules that may have intrinsic pharmacologic activity. Examples of drug with improved taste are given below.[43,44]

Sr. no.	Parent drug	Prodrug with improved taste
1	Chloramphenicol	Palmitate ester
2	Clindamycin	Palmitate ester
3	Triamcinolone	Diacetate ester

Table no.5: Prodrugs with improved taste

The concept of prodrug is widely used in the taste masking of bitter pharmaceuticals, basically in case of children's. The bitterness, acidity or causticity of the drug cause poor patients compliance.

Two approaches can be used to overcome these problems

1) Reduction of drug solubility in saliva.
2) To lower the affinity of drug for taste receptors.

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. 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. Other advantages of prodrugs include change in aqueous solubility, increase lipophilicity, improved absorption, less side effects and change in membrane permeability etc.[45]

4.7. Granulation

Granulation lowers the effective surface area of the bitter substance that come 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. The additional benefit obtained is ease of processing for tablet compression as the majority of drugs have a low bulk density. Additionally, polymers that serve as binders and taste-masking agents may be incorporated, which reduce the perception of taste. Granulation may be achieved with or without the use of a solvent. Dry granulation involves the use of forming compacts/slugs that are milled for blending.

Wet granulation can be achieved by using the fluid bed process or high shear granulation. In the fluid bed process, the drug is suspended in the bed with air, and a binder is sprayed from the top. The granules formed are porous and not amenable to further processing like coating. In high-shear granulation, the granule formation occurs by spraying a liquid binder onto drug/mixture of drugs with excipients that are being agitated by combined action of an impeller and chopper. The

granules obtained are dense and may be used directly or coated further in a fluid bed. This approach is suitable for high-dose drugs (>50 mg) with unpleasant taste. [46,47,48]

4.8. Taste masking by adsorption

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 preparation of adsorbate of bitter drugs. Loperamide and phenyl propanolamine have been adsorbed on magnesium aluminium silicates also known as Veegum F to prepare bitter taste masked suspension of these drugs. [49]

4.9. pH Modifiers

Many drugs are less soluble at pH different from the pH value of the mouth, which are around 5.9. Drugs can be insufficiently solubilized to be available to taste if the equilibrium concentration is below the taste threshold. After a solubilization inhibitor, such as sodium carbonate, sodium bicarbonate, sodium hydroxide, or calcium carbonate, was added to increase the pH when granules including a drug sildenafil dissolved in aqueous medium, the bitter taste of the drug was successfully masked by a sweetener alone .[50] Many natural and synthetic polymers, resins and waxes alone or in combination have been employed for taste masking. The enteric polymers like eudragit L are used for taste masking but the pH of saliva is near 5.8 and these polymers solubilize at pH beyond 5.5 so there is a possibility of drug being partially leached. Therefore there is a need for the development of taste masking polymer such that the bitter taste is completely masked by the polymer at the pH of saliva in mouth and in the reconstitution medium as in case of the liquid orals and further which is able to protect the drug in a biologically active form, from the moisture in the dosage form and releasing the drug rapidly in the stomach without affecting its absorption and bioavailability.[51]

4.10. Multiple Emulsions:

A novel technique for taste masking of drugs employing multiple emulsions has been achieved by dissolving the drug moiety in the inner aqueous phase of w/o/w emulsion with good self life stability. o/w/o emulsion is a type of multiple emulsion in which water globules themselves containing dispersed oil globules, conversely w/o/w emulsions are those in which internal and external aqueous phases are separated by the oil. It is prepared by phase inversion technique or membrane emulsification technique. The formulation is designed to release the drug through the

oil phase in the presence of gastrointestinal fluid. Multiple emulsions is also a good approach for taste masking of bitter drugs. Both types of multiple emulsions are prepared for Chloroquine sulphate and reported to be partially effective in masking the bitterness of the drug. [52]

4.11. Taste Masking with Lipophilic Vehicles like lipids and lecithins

a) Taste masking with lipophilic vehicles

Oils, surfactants, polyalcohols, and lipids effectively increase the viscosity in the mouth and coat the taste buds, and therefore they are potential taste masking agents. Guaifenesin has improved taste when mixed with carnauba wax and magnesium aluminium silicate and then melt-granulated. The taste of cimetidine can be improved by granulating it with glyceryl monostearate. Gabapentin (acyclic amino acid, a drug for seizures) has improved taste when coated with gelatin and then mixed with partially hydrogenated soybean oil and glyceryl monostearate. [53]

b) Taste masking by coating with hydrophilic vehicles

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. A specialized technique, i.e., micro emulsion technology, has been used for taste masking of powders, chewable tablets, and liquid suspensions. [54]

4.12. Development of Liposome:

The term liposome's (meaning lipid body) was derived on the basis of names of sub cellular particles like lysosome and ribosome .It is defined as a spherule/vesicle of lipid bilayers enclosing an aqueous compartment. The lipid most commonly used is phospholipids. Sphingolipids, glycolipids and sterols have also been used to prepare liposomes. 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. Bitter substances are commonly hydrophobic in nature hence lipoprotein composed of phosphatidic acid and β- lactoglobulin can mask the target sites for bitter substances on the taste receptor membrane without affecting responses to salts, acids, sugars or sweet amino acids. Selective inhibitions of bitter taste of various drugs by phospholipids such as phosphatidic acid, phosphatidylinositol, soy lecithin, have been reported.

Bitter taste of polymyxin B sulfate and trimethoprimsulfamethoxazole has been masked by BMI 60 obtained by fractionating soy lecithin.[55,56,57,58]

4.13. Miscellaneous taste masking approaches:

By effervescent agents -

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, flavoring 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 formulation contains 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 -

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 can be formulated with xanthan 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 methonine (stabilizer) and maltitol (thickening agent). Maltitol is stable in range of 2 to 3 and besides masking unpleasant taste of drug, it also inhibit its undesirable local anesthetic effect .

Continuous multipurpose melt (CMT) Technology

The CMT method was developed for the continuous granulation and coating of pharmacologically active substances. It was concluded that this method could be successfully applied for taste masking of bitter drugs. [59,60,61]

5. EVALUATION TECHNIQUES

Sensory evaluation

Taste, to think of, is a very subjective perception. Depending on individuals, the perceived taste may vary to different degrees. If we have well controlled experimental set up, it is possible to

accurately and reproducibly measure taste thresholds. To quantitatively evaluate taste sensation, following methods have been reported in literature

• Panel testing (human subjects)

• Measurement of frog taste nerve responses.

• Multichannel taste sensor/ magic tongue

• Spectrophotometric evaluation/ D30's value

5.1.In-vivo testing

• **Panel Testing**

The panel testing is a psychophysical rating of the gustatory stimuli. In this method, a group of about 5-10 human volunteers is trained for taste evaluation by using reference solutions ranging in taste from tasteless to very bitter. Numerical values are then assigned to these levels of bitterness (eg.,0-5). Subsequently, test solution is tasted and rated on the same scale to assess its bitterness. Literature reports panel testing in invariably all the taste-masked drugs being evaluated. The ease of the method combined with the accuracy of human perception of taste against any other gustatory evaluation technique makes panel testing the most commonly used technique.

• **Measurement of Frog Taste Nerve Responses**

In this method, adult bull frogs are anaesthetized intraperitoneally and the glossopharyngeal nerve is then located and dissected from the surrounding tissue and cut proximally. An ac-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, taste masked by PA-LG(phosphatidic acid-lactoglobulin) combination have been reported to be evaluated by this technique.

5.2. In-vitro testing-

• **Spectrophotometric Method** A known quantity of the taste-masked formulation is mixed with 10 ml of distilled water in 10 ml 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 evalute the taste masked granules of sparfloxacin, with threshold concentration being 100µg/ml.

Electronic tongue:

This is also called multichannel taste sensor or magic tongue. This is an automated taste sensing device to detect the magnitude of bitterness of drug substance. The device has a transducer which is composed of several kinds of lipid/polymer membranes with different characteristics that can detect taste in manner similar to human gustatory sensation. Taste response is transferred into a pattern composed of electric signals of membrane potentials of the receptor part. Different response electric potential pattern are obtained for substances producing different taste qualities. Recently, the technique has been applied, for the quantitative evaluation of the bitterness of some commercially available medicines. Quinine hydrochloride was taken as the standard for bitterness. Basic drug with amino groups in the molecule such as quinine, show a comparatively good correlation between the relative response electric potential (mV) of channels 1 or 2 of the taste sensor, which contain negatively charged membranes, and the bitterness as determined by human gustatory sensations tests. [62,63,64]

CONCLUSION

With application of these techniques one can improve product preference to a large extent. In addition to oral drug delivery, the taste masked drug delivery research is gaining importance for the quality of the treatment provided to patients, especially children and old. As evidenced by number of patients and technology developments, an attempt of ideal taste masking is widely accepted in the development of palatable dosage forms having good patient compliance without interfering the drug release. Involve least number of equipment's and processing steps, require minimum number of excipients for an optimum formulation, no adverse effect on drug bioavailability, require excipients that are economical and easily available, least manufacturing cost, can be carried out at room temperature, require excipients that have high margin of safety, rapid and easy to prepare.

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