Taste masking method for bitter drug and tasteless dispersible tablet: an overview

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Introduction

The problem of bitter and obnoxious taste of drug in pediatric and geriatric formulations is a challenge to the pharmacist in the present scenario. In order to ensure patient compliance bitterness masking becomes essential. Molecule interacts with taste receptor on the tongue to give bitter, sweet or other taste sensation, when they dissolve in saliva. This sensation is the result of signal transduction from the receptor organs for taste, commonly known as taste buds. These taste buds contain very sensitive nerve endings, which produce and transmit electrical impulses via the seventh, ninth and tenth cranial nerves to those areas of the brain, which are devoted to the perception of taste (1). Two approaches are commonly utilized to overcome bad taste of the drug (2). The first includes reduction of drug solubility in saliva, where a balance between reduced solubility and bioavailability must be achieved. Seen approach is to alter the ability of the drug to interact with taste receptor. An ideal taste masking process and formulation and characterization should have the following properties (3).

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.

Methods of Taste Masking

Various methods are available to mask undesirable taste of the drugs. Some of these are as given below.

1. Coating of drug particles with inert agents

Coating is an extremely useful technique for number of applications in the pharmaceutical field. By coordinating the right type of coating material it is possible to completely mask the taste of a bitter drug, while at the same time, not adversely affecting the intended drug release profile.(4) Any nontoxic polymer that is insoluble at pH 7.4 and soluble at acidic pH, would be an acceptable alternative for taste masking. Taste masking of ibuprofen has been successfully achieved by using the air suspension coating technique to form microcapsules, which comprises a pharmaceutical core of a crystalline ibuprofen and methacrylic acid copolymer coating that provides chewable taste masked characteristics.(5) Various inert coating agents like starch; povidone, gelatin, methylcellulose, ethyl cellulose etc. are used for coating drug particles. One of the most efficient methods of drug particle coating is the fluidized bed processor. In this approach powder as fine as 50µm, are fluidized in expansion chamber by means of heated, high velocity air and the drug particles are coated with a coating solution introduced usually from the top as spray through nozzle. The coated granules are dried with warm air.(6)

2. Taste masking by formation of inclusion complexes

In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent i.e., the host molecule forming a stable complex. The complexing agent is capable of masking the bitter taste of the drug 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. Vander Waals forces are mainly involved in inclusion complexes.(7) Beta-cyclodextrin is most widely used complexing agent for inclusion type complexes. It is sweet, nontoxic, cyclic oligosaccharide obtained from starch. Strong bitter taste of carbapentane citrate syrup was reduced to approximately 50% by preparing a 1:1 complex with cyclodextrin.(8) The suppression of bitter taste by cyclodextrin was in increasing order of alpha, gamma, and beta cyclodextrin.

3. Molecular complexes of drug with other chemicals

The solubility and adsorption of drug can be modified by formation of molecular complexes. Consequently lowering drug solubility through molecular complex formation can decrease the intensity of bitterness of drug. (9) reported that caffeine forms complexes with organic acids that are less soluble than xanthane and as such can be used to decrease the bitter taste of caffeine.(8)

4. 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.(10) Solid dispersion is also called as co precipitates for those preparation obtained by solvent method such as co precipitates of sulphathiazale and povidone. Solid dispersions using insoluble matrices or bland matrices may be used to mask the bitter taste of drugs. Also using them as absorbents on various carriers may increase the stability of certain drugs.

5. Microencapsulation

Microencapsulation as a process has been defined by as a means of applying relatively thin coating to small particles of solid, droplets of liquid and dispersion. This process can be used for masking of bitter tasting drugs microencapsulating drug particles with various coating agents. Coating agents employed includes gelatin, povidone, HPMC, ethyl cellulose, Bees wax, carnauba wax, acrylics and shellac. Bitter tasting drugs can first be encapsulated to produce free flowing microcapsules, which can then be blended with other excipients and compressed into tablets. Microencapsulation can be accomplished by variety of methods including air suspension, coacervation, phase separation, spray drying and congealing, pan coating, solvent evaporation and multiorifice centrifugation techniques.(11)

6. Multiple Emulsions

A novel technique for taste masking of drugs employing multiple emulsions has been prepared by dissolving drug in the inner aqueous phase of w/o/w emulsion under conditions of good shelf stability. The formulation is designed to release the drug through the oil phase in the presence of gastrointestinal fluid.(12,13)

7. Prodrugs

A prodrug is a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent drug. Examples of drug with improved taste are given below

Table no.1: Prodrugs with improved taste

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

8. Mass extrusion method (Dispersion coating)

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.(14)

9. Ion Exchange Resin

Another popular approach in the development of taste masking is based on ion exchange resin. 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 resulting ion exchange is reversible and stiochiometric with the displacement of one ionic species by another.(15) Synthetic ion exchange resin have been used in pharmacy and medicine for taste masking or controlled release of drug as early as 1950.(16,17) Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert. The long-term safety of ion exchange resins, even while ingesting large doses as in the use of cholestyramine to reduce cholesterol (17) is established unique advantage of ion exchange resins is due to the fixed positively or negatively charged functional groups attached to water insoluble polymer backbone. The adsorption of bitter drugs onto synthetic ion exchange resins to achieve taste coverage has been well documented. Ion exchange resins like Amberlite CG 50 was used for taste masking of psedoephedrin in the chewable Rondec decongestant tablet.(17) Antibacterial belonging to quinolone category like ciprofloxacin was loaded on cation exchanger and administered to animals. The taste was improved as animal accepted the material more readily.(18) binding to a cation exchange resin like Amberlite IRP-69 masked the taste of peripheral vasodilator buflomid. Manek S.P.et al. evaluated resins like Indion CRP 244 and CRP 254 as taste masking agents. Some bitter drugs whose taste has been masked by using ion exchange resin are listed in the table no.2.

Table No.2: Bitter Drugs masked by ion exchange resin

Drug	***Ion exchange resin***
Norfloxacin	Indion 204 (weak cation exchange resin)
Ciprofloxacin	Indion 234 (weak cation exchange resin)
Roxithromycin	Indion 204 (weak cation exchange resin)
Chloroquine phosphate	Indion 234 (weak cation exchange resin)

Ion exchange resins (IER) have received considerable attention from pharmaceutical scientists because of their versatile properties as drug delivery vehicles. In past few years, IER have been extensively studied in the development of Novel drug delivery system and other biomedical applications. Several ion exchange resin products for oral and peroral administration have been developed for immediate release and sustained release purposes. Research over last few years has revealed that IER are equally suitable for drug delivery technologies, including controlled release, transdermal, nasal, topical, and taste masking.

Table No.3: Taste masking by polymer coating

S.No.	drugs	technique	Polymer used	Ref. no.
1	Pinaverium bromide	coating	Cellulose or shellac	20
2	Propantheline bromide	coating	L-HPC,EC	20
3	Ibuprofen	Air-suspension coating	Methacrylic acid co-polymer(Eudragit)	21
4	Triprolidine HCL	Dispersion coating	HPMC	22
5	Dimenhydrinate	-	Eudragit or CMC	23
6	Cefeanel daloxate HCL	Granulation and coating	PVP,EC,HPMC	24
7	Enoxacin	-	HPMC,HPC,EC	25
8	Sparfloxacin	-	HPMC,HPC,EC, L-HPC	26,27
9	Aspirin	Rotagranulation and coating	Cellulose acetate latex and triacetine	28
10	Famotidine	-	HEC,HPMC	29
11	Amoxicillin trihydrate	Granulation	MCC,L-HPC	30
12	Acetaminophen	coating	Cellulose acetate,HPC/cellulose acetate,Eudragit E100,PVP	31,32
13	Morphine HCL	-	Cellulose,Eudragit NE 30D	33,34
14	Amiprilose HCL	-	Calcium gluconate, Calcium alginate	35
15	Terfenadine	Mixing	Sodium alginate,carrageenamand macrogol-400	36
16	Beclamide	Microencapsulation	Gelatin	37
17	Clarithromycine	Rotagranulation	Carbopol,PVP	38
18	Roxithromycin	Granulation and coating	PEG,EudragitL 100-55	39
19	Nizatidine	Spray drying	Eudragit E 100	40
20	Cetraxate HCL	Melt granulation and coating	Corn starch,Macrogol-6000	41,42
21	Ciprofloxacin	Microencapsulation	Eudragit NE30 D	43
22	Pirenzepine and Oxybutynin	Dispersion coating	Eudragit E-100,MCC, HPC	44
23	Diclofenac	Microencapsulation	Ethyl cellulose	45
24	Nicorandil	Coating	Crosscarmellose	46,47

			sodium,D-mannitol,lactose	
25	Levofloxacin	coating	Eudragit E-100 ,cellulose acetate	48,49
26	Cefuroxime axetil	Emulsion-solvent evaporation	Eudragit L-55a and RL	50

Recent approaches and development of taste masking: Development a taste masked microcapsules composition for oral administration of a drug. The composition compromise microcapsules of a drugs and substantially water-insoluble polymeric material, typically a cellulose polymer (ethyl cellulose).(51-52) Taste masking was done phase separation coacervation, emulsion solvent diffusion technique in which the drug was coated with relatively high level of polymeric material. These high coating levels gives rise to effective taste masking, while the never less allowing targeted release of drug, so the drug was release shortly after passages through the mouth microcapsules were evaluated for flow, color, odor, mouthfeel/grittiness, taste-masking, bitterness, after taste and overall acceptance. (53-58) The microcapsules composition may be incorporated into any number of pharmaceutical formulations, including chewable tablets, effervescent tablet powders, liquid dispersion dispersible tablet.(59) Dispersible tablet: These are tablets that disintegrate within three minutes to form a suspension with a pleasant taste when placed in a small amount of water, e.g. in a tablespoonful or a glass of water. However, they can also be placed directly on the tongue and sucked.(60) Advantages of dispersible tablets· They are ease to swallow, so they are particularly suitable both for elderly persons with swallowing difficulties and for children.(61) · They have quicker onset of action. (62) ·Certain dispersible tablet's can also be divided.(62) · The bitter taste of the active substances must be masked in advance. · Owing to the number of possible applications, the patient compliance is improved.

Techniques Employed for Making Continues Dosage Forms

The drug i.e. the active pharmaceutical ingredient is finally formulated in a suitable dosage form such as tablet, powder, liquid, etc. Tablets: Most of the tablets can be effectively masked for their taste by applying inert polymer coatings that prevent the interaction of the drug substance with the taste buds. Nevertheless, attempts have been made time and again by several workers to investigate and explore the use of newer materials in bad taste abatement and good taste enhancement.(62) Powder: Have reported a granular composition for taste masking comprising of drug core of a NSAID and methacrylate ester copolymers as coating agents for taste masking. The method comprises of coating the drug cores with separate layers of aqueous dispersions of the copolymers. Granules of the invention could be used in the preparation of chewable tablets, which had good palatability and bioavailability.(63) Evaluation of Taste Masking Effect Sensory analysis has been used in developed countries for years to characterize flavors, odors, and fragrances. Historically expert provided formulation scientist with subjective data on the composition of one product with another. Nowadays, sensory analysis employs objective or analytical methods. Invented a multichannel taste sensor whose transducer is composed of several kinds of lipid/polymer membrane with different characteristics, which can detect taste in manner similar to human gustatory sensation. Taste information is transformed into a pattern composed of electrical signals of membrane potential of the receptor part. It was reported that suppression of bitterness of Quinine and a drug substance by sucrose could be quantified by using multi channel taste sensor. The present method can be expected to provide new automated method to measure the strength of drug substance in place of sensory evaluation. Evaluation of the taste masking effect from coated microsphere can be done by determining the rate of release of the drug from the microspheres. Similarly for evaluating the taste masking effect by ion exchange resin, the drug release rate can serve as an index of the degree of masking achieved. Other methods include evaluation by a trained flavor profile panel and time intensity method in which a sample equivalent to a normal dose was held in mouth for 10 seconds. Bitterness level are recorded immediately and assigned values between 0-3 (64).

Taste assessment:

Taste assessment one of the important quality control parameters for evaluation of taste masked formulation .Drug or formulation can be asses using in vivo and in vitro method of taste evaluation parameters.

In vitro approaches for taste assessment

Release studies are commonly used in taste assessment. To measured the effectiveness of coating and comlexation within a formulation. They are indirect methods for assessing taste because the method does not contribute to the evaluation of taste and sweetness of the drug product. Novel drug release apparatus and pharmacopoeial apparatus have both been adapted to stimulate buckle dissolution of dosages forms so compare taste in different pharmaceutical formulation such novel apparatus and method or drug dissolution are release studies tend to stimulate the release of bitter or undesirable tasting drug in the mouth. In vitro approaches taste assessment In vitro drug release studies: Pharmacopoeial release studies taste have been modified by altering the chemical composition of the dissolution media (e.g. artificial saliva) and reducing the size of the basket screen size (screen size< 0.381 mm square opening) to prevent particles forms escaping. Taste masking is achieved when, in the early time points forms 0-5 min. the drugs substances in the dissolution medium is either not detected or amount is below the threshold for identifying its taste. Drug can be analyzed either spectrophotometrically or using HPLC. Of these HPLC is generally preferred especially when testing is performed in the presences of UV-absorbing component, such as flavorings and sweetener. A novel in vivo buckle dissolution testing apparatus and method for the assessment of taste masking in oral dosages forms have recently been invented. The apparatus consists of a single, stirred, flow-through filtration cell including a dip tube designed to remove fine solid particles. Simulated saliva is used as the dissolution medium. The filtrated solution is removed from the apparatus continuously and used to analyze the dissolve drug.

1. Voltramettric electronic tongue

The Voltramettric electronic tongue developed by s-*sense consistent of four working metal electrode made of gold, platinum, iridium and rhodium an Ag/AgCl references and a stainless steel counter electrode. A relay box enables the working electrode to be connected conseculevily, to form four standards three-electrode configurations. The potentially pulse are applied by a potentiostat which is controlled by a personnel computer. the PC used to set and control the pulse, measure and store current response, and to operate the relay box.

2. Electronic tongue developed by the university of taxes and visions

The electronic tongue initially developed by the University of Taxes consists of a light sources, a sensors array and detector. The light sources shines onto chemically adapted polymer beads arranged on a small silicon wafer, which is known as a sensors chip the beads change is color on the basis of the presences and quality of specific chemical. The change is color is capture by a digital camera and the resulting signal converted into data using video capture board and a computer. In vivo approaches for taste assessment: In vivo studies, stimuli are applied on to the tongue of either human or animals.

1. Humane taste panel studies

Human taste panel studies evaluated tastant (food, chemical, drug and so on) by estimating the gustatory sensation response in healthy human volunteers within well-controlled process. Such studies are there for also known as physiological evaluation, gustatory sensation testes or taste trials. They are sensitively measured of taste and are spastically designed to minimize bias and response within and between human volunteers. Well-established methodology for performing sensory analysis can be broadly divided into five types, namely discrimination taste. Scaling taste, experts testers, affective taste and descriptive methods and have been excellency discussed. Volunteers asses the taste quality and intensity of standard are taste stimuli on different adjective scales including various properties of the sample, such as overall intensity, sweet, odor, bitter, metallic, cooling, hot, spicy, anesthetic,

astringent etc. Each adjective can be rated on an intensity scale ranging from zero to four or perhaps even up to nine points on provided score sheets.

2. Animal preference testes

Bottle performance and condition taste aversion taste are used for taste for determining taste preference and concentration-response properties of tastant by animal 3 and 4 rats, mice, cats and dogs can be used for the potentiometrically e-tongue, incorporating and array of artificial lipid-polymer membranes as a fingerprint devices, has been developed as a promising tool for use in the quality control of phytomedicines. The miniaturization of taste sensors is particularly interest for the food and pharmaceutical industries. A portable low-cost sensing system has been made that interfaces to a Voltramettric electronic tongue sensors. Screen-printing technologies have been used to developed a disposable taste sensors.(65)

Conclusion:

Taste masking of bitter drugs has been a challenge to the scientist. We have made an attempt to describe various methods, which could be suitable for taste masking of bitter drugs. The methods described in this review can be used for bench scale as well as pilot scale also. (66) There are numbers of technologies available which effectively mask the objectionable taste of drugs but require skillful application which does not affect the bioavailability of drug.(67) Recent trends of patient oriented practice demand design of patient oriented dosage form to achieve patient compliance. Taste masking of bitter drugs has significantly improved the quality of treatment provided to suffering patient, especially children.

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