INTERNATIONAL JOURNAL OF DECCAN PHARMA AND LIFE SCIENCES

www.ijdpls.com

(Original Article)

Received: 25-07-2012; Revised; Accepted: 08-08-2012

A OVERVIEW ON TASTE MASKING OF BITTER DRUGS

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Keywords:

Taste, Taste-masking, Oral pharmaceuticals, pediatric patients, bitter drugs

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ABSTRACT

Taste is one of the most important parameters governing patient compliance. Undesirable taste is one of several important formulation problems that are encountered with certain drugs. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients. Several oral pharmaceuticals, numerous food and beverage products, and bulking agents have unpleasant, bitter-tasting components. So, any pharmaceutical formulation with a pleasing taste would definitely be preferred over a competitor's product and would translate into better compliance and therapeutic value for the patient and more business and profits for the company. The desire of improved palatability in these products has prompted the development of numerous formulations with improved performance and acceptability. This article reviews the earlier applications and methodologies of taste masking and discusses the most recent developments and approaches of bitterness reduction and inhibition for oral pharmaceuticals.

INTRODUCTION

There are numerous pharmaceuticals that contain actives, which are bitter in taste. With respect to OTC preparations, such as cough and cold syrups, the bitterness of the preparation leads to lack of patient compliance. 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. Another approach is to alter the ability of the drug to interact with taste receptor. An ideal taste masking process and formulation should have the following properties**.** [(3)]

Involve least number of equipments 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.

PHYSIOLOGY & PSYCHOLOGY OF TASTE

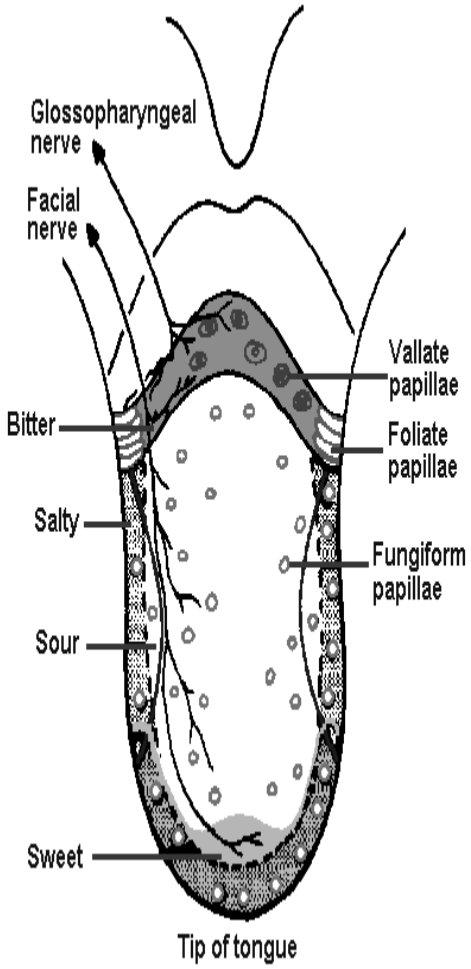
To obtain an understanding of the reasoning behind this research, a basic understanding of the physiological and psychological events that occur simultaneously in the experience known as taste is necessary. The earlier teaching of a taste map of the tongue showing distinct areas responding to certain stimuli has been replaced with a new

theory. The most recent theory is that all taste buds respond to all stimuli. These stimuli include sweet, sour, bitter, salt.

Taste buds are onion-shaped structures containing between 50 to 100 taste cells.[1] Chemicals from food or oral ingested mendicants are dissolved by the saliva and enter via the taste pore. There they either interact with surface proteins known as taste receptors or with pore-like proteins called ion channels. These interactions cause electrical changes within the taste cells that trigger them to send chemical signals that translate into neurotransmission to the brain. Salt and sour responses are of the ion channel type of responses, while sweet and bitter are surface protein responses. The electrical responses that send the signal to the brain are a result of a varying concentration of charged atoms or ions within the taste cell. These cells normally have a net negative charge. Tastants alter this state by using varying means to increase the concentration of positive ions within the taste cell. This depolarization causes the taste cells to release neurotransmitters, prompting neurons connected to the taste cells to relay electrical messages to the brain.[(2)] In the case of bitter taste, such as quinine, stimuli act by binding to G-protein coupled receptors on the surface of the taste cell. This then prompts the protein subunits of alpha, beta, and gamma to split and activate a nearby enzyme. This enzyme then converts a precursor within the cell into a "second messenger." The second messenger causes the release of calcium ions (Ca++) from the endoplasmic reticulum of the taste cell. The resulting build-up of calcium ions within the cell leads to depolarization and neurotransmitter release. The signal now sent to the brain is interpreted as a bitter taste. [(3)]

Based upon the recent theory that taste cells can interpret and process all the different stimuli, a method of diminishing the overall response to one stimulus would be to introduce a second stimulus. This is based upon the assumption that differences among responses to stimuli are not so much a distinction between firing and non-firing of the neurons, but instead the difference in the amount of firing. [(4)] This theory is the basis for the current research being presented in this paper: the ability to transform the responses of certain

stimuli by introducing other stimuli. Effective blocking of the taste receptors can be accomplished by either coating the surface pore or competing within the channel themselves to reduce the net effect of the bitter stimuli firings. While the introduction of competing stimuli is part of the masking system, specific flavors and sweetness profiles are essential to complete the experience and produce a pleasant taste for the consumer.



METHODS OF TASTE MASKING

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

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 meth acrylic acid copolymer coating that provides chewable taste masked characteristics. [(5)]

Various inert coating agents like starch; providence, gelatin, methylcellulose, ethyl cellulose etc. are used for coating drug particles. One of the most efficient method of drug particle coating is the

fluidized bed processor. In this approach powder's 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]

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 oligosacchride 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 cyclodextrin.

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. 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]

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 absorbates on various carriers may increase the stability of certain drugs.

MICROENCAPSULATION

Microencapsulation as a process has been defined by Bokan 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 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, multiorifice centrifugation techniques**.** [(11)]

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)]

USING LIPOSOME'S

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 in HEPES (N-2-hydroxyetylpiperzine-N'- 2- ethane sulfonic acid) buffer at pH 7.2. [(14)]

PRODRUGS

A prodrug is a chemically modified inert drug, which upon biotransformation liberates the pharmacologically active parent drug. Examples of drug with improved taste are given below. [(2)]

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

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]

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 were 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.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.

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.

Technical Challenges in Taste-Masking

At Aptalis Pharmaceutical Technologies, our teams of scientists understand the complex relationship between the taste of an active pharmaceutical ingredient (API) and its physiochemical properties.

Factors that are taken into consideration during taste-masking formulation process include:

- Extent of the bitter taste of the API
- Required dose load
- Drug particulate shape and size distribution
- Drug solubility and ionic characteristics
- Required disintegration and dissolution rate of the finished product
- Desired bioavailability
- Desired release profile
- Required dosage form

Our formulation experts balance these factors against the product's desired organoleptic (sensory) properties such as taste, mouth-feel, size and weight of the pill in order to create a 'patient-friendly' product for our partners to bring to market.

CONCLUSION

The popularity of FDTs has increased tremendously over the last decade. There are about 40 drugs that have been formulated into marketed FDTs using various technologies (Table 2). The key to FDT formulations is fast disintegration, dissolution, or melting in the mouth, and this can be achieved by producing the porous structure of the tablet matrix or adding superdisintegrant and/or effervescent excipients. FDTs prepared by direct compression usually have good mechanical properties, and the strength can be enhanced further by subsequent treatment, such as moisture treatment. The clinical studies show FDTs can improve patient compliance, provide a rapid onset time of action, and increase bioavailability. Considering the many benefits of FDTs, it is only a matter of time until a majority of oral formulations are prepared in FDT forms.

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