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Taste masked dry syrup: a review

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ABSTRACT

Oral route of drug administration has been one of the most convenient and accepted route of drug delivery and amongst it the intraoral route is the most preferred due to its convenience and rapid onset of action. Intraoral dosage forms have evolved as an alternative to conventional tablets, capsules and liquid preparations. There is an important category of suspension that is available as dry powders intended for suspension in liquid vehicles. These are dry mixtures containing the drug and suitable suspending and dispersing agents to be diluted and agitated with a specific quantity of vehicle, most often purified water. Drugs that are instable if maintained for extended periods in the presence of aqueous vehicle (eg., many antibiotic drugs) are frequently supplied as dry powder mixtures for reconstitution at the time of dispensing. This type of preparation is designated in the USP by a title "for Oral Suspension". The reconstituted system is the formulation of choice when the drug stability is a major concern. After reconstitution, these systems have a short but acceptable life if stored at refrigerator temperatures. Re-constitutable oral systems show the adequate chemical stability of the drug during shelf life, avoids the physical stability problems related to solubility, pH and incompatibilities with other ingredients and also reduce the weight of the final product because the aqueous vehicle is absent and consequently the transportation expenses may be reduced.

Keywords: Taste masking; Dry syrup: Taste buds; Liquid oral Suspension

INTRODUCTION

The concept of bitter taste are more efficient has been reversed with development of numerous formulation techniques. In recent era oral administration of bitter drugs with an acceptable degree of palatability becomes key issue for the health care providers, especially for pediatric and geriatric patients. Palatability is the combination of sensory perceptions including taste and smell and to a lesser extent texture, appearance and temperature of the products. Taste transduction involves the interaction of molecule with taste receptor cells, which reside in specific structures known, as Taste Buds. The function of taste buds is to relay information about the taste of the molecule to the central nervous system. Each taste type affects the receptor cells through distinct mechanisms. The transduction of most bitter and sweet compounds is mediated by G protein gustducin while for salty and sour, is done by ion channels. Dissociation of gustducin into alpha and beta subunit decreases cAMP level and activate phospholipase C, which generates second messenger IP3 and DAG. This complex cascade of bio chemical events results in taste cells sending a signal to the brain that is

interpreted as bitter and unpleasant. Thus preventing interaction between active molecule and taste bud could mask bitter taste.

Numbers of therapeutically active herbal molecules are having bitter taste. The unpleasant and unacceptable taste can be modified using below mentioned suitable techniques. Since last two decades large numbers of industrially viable techniques, are very well explored for the taste masking of bitter drugs. The present article gives an overview of past and current scenario of taste masking techniques [1, 2].

The physiology of taste buds

Taste buds are onion-shaped structures containing between 50 to 100 taste cells. The active ingredients taken orally in liquid/ uncoated/ mouth dissolve dosage forms first come in contact with oral cavity where they get 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 [3, 4].

Taste-masking by increase in viscosity

The formulations prepared using viscosity imparting agents such as gums or carbohydrates can lower the contact with taste buds and diffusion of bitter substances from the saliva to the taste buds. This methods has been use for taste masked liquid preparation containing relatively large amount of unpleasant tasting medicines. The composition of such a formulation comprises a taste-masking liquid base with a high viscosity induced by thickening agents such as polyethylene glycol and sodium carboxy methylcellulose. This type of formulations can incorporate higher amount of active ingredient then regular strength. For example, guaifenesin, which is normally administered in doses of not more than 100 mg in 5 ml of liquid, may be administered in doses of 200 mg/5 ml, without the feel of bitter taste [5, 6].

Taste masking using lipids

Oils, surfactants and polyalcohols can effectively increase viscosity in the mouth and prevent contact of drug with taste buds. Taste masking of chloroquine was masked using the same principal. Multiple emulsions, O/W/O, containing paraffine as oil could mask bitter taste of chloroquine to some extent. Using glyceryl diester of C6- C22 fatty acid or diglycerine or sucrose fatty ester bitter taste of oral pharmaceuticals could be controlled. An aqueous solution containing quinine sulphate with diglyceride from rapeseed oil and sucrose with ester did not taste bitter. Hence, any excipient, which can impart viscosity in mouth and coating of taste buds, can successfully used for taste masking. Formulations with a large excess of lecithin or lecithin-like substances are claimed to control bitter taste in pharmaceuticals. Magnesium aluminum silicate with soybean lecithin is used to mask the unpleasant taste of talampicillin HCl. Lipid coated pellets has also been studies for taste masking of hydrophobic drugs [7, 8].

Taste masking using anesthetic agents and taste potentiators

The taste buds can temporarily be anesthetized using local anesthetic agents like phenol and phenolic derivatives. These agents cause numbness of taste buds and hence the sensory buds will not be able to recognize the bitter taste. However, the time period for this numbness remains for 4 to 5 second. Fine powder of bees wax, sodium phenolate and active substance mixed with crosco vegetable oil, lime floss sugar and converted into lozenges. This formulation produced numbness of taste buds [9].

Taste masking with salt preparation

Salt preparations have been successfully used to mask the taste by decreasing the solubility of drug into saliva or by altering the chemical group,

which is responsible for bitter taste. Most salts of organic compounds are formed by the addition or removal of proton to form an ionized drug molecule, which is then neutralized with a counter ion. Penicillin prepared as the N-N' dibenzylethylene diamine acetate salt is a tasteless material. Magnesium salt of aspirin is almost tasteless. Bitter tasting decongestants, antihistamines, antitussive expectorants effectively taste masked using magnesium trisilicate/ fumed silica absorbate that is undetectable in mouth yet provides high degree of bioavailability. The unpleasant taste of water soluble Ibuprofen was masked by preparing alkaline metal bicarbonate salt of Ibuprofen [10, 11].

Taste masking with effervescent formulations

Effervescent formulation contains components that can produce effervescence, like sodium bicarbonate, due to liberation of carbon dioxide. Sodium bicarbonate reacts with the acid when the effervescent preparation is added to water. The solution remaining after effervescence is known as carbonated water. The medicament dissolves in the carbonated water which serves to mask bitter, saline or nauseous taste of medicament. Studies carried out on effervescent granules of cetrizine showed better patient compliance [12, 13].

Taste masking by prodrug formulation of the drug

A prodrug is a chemically modified inert drug precursor that upon biotransformation liberates the pharmacologically active drug. By changing the molecular configuration of the parent molecule, the magnitude of a bitter taste response or taste receptor-substrate adsorption constant may be modified. Prodrugs can be used to increase or decrease the aqueous solubility, mask bitterness, increase lipophilicity, improve absorption, decrease local side effects, and alter membrane permeability of the parent molecule. For example 7-7, succinyl-ditheophylline. Erythromycin estolate. In aqueous solution, erythromycin exists as protonated form which has solubility in water. Lauryl sufate salt of Erythromycin estolate, a prodrug, is water insoluble. It does not impart bitter taste when comes in contact with taste buds unlike parent drug. The palmitate ester of chloramphenicol, a prodrug, used in pediatric suspension shows good patient compliance. Some other examples include propoxyphen napsylate, tasteless and sparingly soluble derivative of Propoxyphen, clindamycin-2 palmitate, a prodrug of clindamycin [14, 15].

Coating techniques

Coating is one of the most industry friendly processes for taste masking. Numbers of bitter drugs are formulated as coated dosage forms. In coating process, core material is coated with appropriate materials which prevents rapid release of the drug in saliva, but allow release of drug in the gastrointestinal tract where the drug is expected to be absorbed. Coating not only masks the taste but also improves patient compliance by improving aesthetic quality.

Coating with sugar solution is one of oldest technique for taste masking. Drug could be granulated along with hydrophilic vehicle and prepared granules can be coated with sugar to serve the purpose of taste masking. The study was carried out for masking the bitter taste of Cefeanal daloxate HCL. Granules of lactose and cornstarch containing Cefeanal daloxate HCL were prepared by using ethanolic solution of polyvinyl pyrrolidine and then coated with ethyl cellulose. They were further coated with coating solution containing lemon oil, sodium saccharine, and sucrose and hydroxypropyl cellulose. The prepared granules were evaluated and results showed good bioavailability and no bitterness. Protein solution could also be used as coating material. Aqueous whey protein solutions containing plasticizers, glycerol and sorbitol and maltodextrin as film formation promoting agent, were used as coating material for taste masking of bitter constituent [16, 17].

Taste masking by solid dispersion

The solid dispersion of one or more drugs in an inert carrier of solid state is prepared by physical mixing, co-grinding or by solvent evaporation method. Inert carriers that can be used for solid dispersion preparation are sugar carriers like sucrose, galactose, dextrose, trehalose, Various PEG derivatives or PVP. Here the drug is entrapped in carrier, so it prevents the contact of the drug with the taste buds. The mass of the drug griseofulvin was prepared using malt dextrin as a

hydrophilic carrier by common solvent method or melting method followed by drying in dessicator over anhydrous CaCl2, and then product is crushed, pulverized and sealed. The resulted formulation was taste masked. The above-mentioned method was used for masking the bitter taste of anti histaminic i.e. femotidine also. The bitter drug femotidine and sugar alcohol and were mixed and the mixture was processed to form solid pharmaceutical preparation. The model bitter drugs Acetaminophen, ketoprofen and trypsinogen were also successfully masked by using Polyethylene glycol (PEG), Eudragit RS (EU) and lipid tripalmitin (TP) as excipients. An excipient and a drug (typically 50% drug loading, 10.0 g batch) were plastisized and then mixed with supercritical CO_2 at operating pressure between 200 – 300 bar and temperature between 40 – 55^0 C. This resulted into polymeric mixtures with taste-masked formulation [18, 19].

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 drug. Complexation of drug with complexing agent modifies the biopharmaceutical parameters like drug dissolution rate and thus it masks the bitterness of the drug. Cyclodextrin (CD) is the most widely used complexing agent. Cyclodextrins are cyclic oligosaccharides, 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. Reconstituted suspension of the CD-drug complex can be prepared for pediatric and geriatric patients. The drug: CD complex can also be directly compressed to prepare orodispersible tablet when fast onset of action of bitter drug is required [20].

Taste masking by ion exchange resin

The complex of cationic drug and weak ion exchange resin does not break at pH of saliva but at high cationic concentration in stomach free drug is immediately released. Thus while passing through mouth, the drug remains in complex form and thereby imparting no bitter taste in the mouth. The peripheral vasodilator buflomedil was taste masked by bonding to a cation exchange resin such as Amberlite IPR 69 at 60% resinate powder. The Amberlite IRP 64 resin powder is also recommended with isopropyl alcohol as solvent. The dried powder was incorporated into oral formulation. The same technique was used in order to formulate taste-masked formulation of clarithromycin. Ion-exchange resin complex was prepared by dispersing clarithromycin in cacao fat at 35 to 50°C and atomizing to get fine granules and then suspended in of poly vinyl acetate diethyl amino acetate at 0°C, spray dried and tested for taste masking. The results showed good bioavailability and no bitter taste. Complex of diphenhydramine with polyglutamic acid was found to be stable in acidic solutions but dissolved gradually as solution pH increased and thus taste of the drug was masked in mouth. Drug-resin complex dissolves completely in a pH=7.4 solution within 5~10 minutes. The ion exchange resin drug complex can be compressed to prepare orodispersible tablet for drugs like levocetrizine dihydrochloride. In this technique the drug resinate complex was prepared by dispersing drug solution in resinate solution, Tulsion 335, for 360 minutes at various temperature between 25º C-80º C and then filtered through whatman filter paper. Solvates were evaporated to get dry powder. The dried drug: resin complex powder was then compressed to form orodispersible tablet. Here, the drug, which gets disprsed in mouth, will not show any bitterness due to its complexation with resin molecule [21, 22].

Dry syrups

These are commercial dry mixtures that require the addition of water at the time of dispensing. A number of official and commercial preparations are available as dry powder mixtures or granules that are intended to be suspended in water or some other vehicle prior to oral administration. Most of the drugs prepared as a dry suspension for oral suspension are antibiotics. The dry mix of oral suspension is prepared commercially to contain the drug, colorants, flavours, sweeteners, stabilizing agents, suspending agents and preserving agents

that may be need to enhance the stability of the formulation.

The granules in the sachets must be taken as a suspension in a glass containing prescribed amount of ingestible liquid, mostly water. Although studies have demonstrated that the dry oral suspension after constitution in a liquid is stable for 24 hours after preparation, it is recommended that the suspension should be consumed immediately after preparation [23].

Advantages of dry syrup

- Accurate single dosing: Single dose sachets
- Sachets: 4 layered aluminium foils making the formulation extremely stable and convenient to carry.
- Enhanced convenience of single dosage regimen.
- Coloured, flavoured, sweet to taste formulation administration among pediatric patients.

Major application

Oral Route of administration is the route of choice for administration of medicines in children. The only hurdle for dosage form designing for pediatric patients is the patient's acceptance of the dosage form. Pediatric Patients tend to become un-co-operative during the administration of oral medication; the most common reason being the taste of the oral formulation administered among the children.

Most of the drugs administered as granules for oral suspension under pediatric therapy are Antibiotics, which when administered orally as any other dosage form have a bitter taste making it unpleasant for Children to consume the medication [24].

The solution for this is Taste masking and the major application of taste masking can be observed in Granules for oral suspension.

Dry oral suspensions advantages over liquid oral suspensions

- Accurate single dosing: Single dose sachets
- Drug dose is comparatively independent of any physical factors i.e. temperature, sedimentation rate and liquid flow properties
- Sachets: 4 layered aluminium foils making the formulation extremely stable and convenient to carry.
- Enhanced convenience of single dosage regimen.
- Coloured, flavoured, sweet to taste formulation administration among pediatric patients.
- Palatable and widely accepted in Pediatric patients all over the world.
- Stability: Stable on storage and when constituted with an ingestible liquid for administration, the corresponding liquid suspension is stable for the duration in which the therapy is required.

Disadvantages of liquid oral suspensions

- Bulk formulation- inaccurate single dosing
- Drug Dose dependent on various physical factors of the dosage form including:
- Temperature of storage
- Sedimentation rate of the formulation
- Liquid flow properties-viscosity, pourability, redispersion, flocculation
- Content uniformity
- Stability of the liquid suspension largely depends on the temperature of storage
- Caking upon storage

Required characteristics of suspensions for reconstitution

Required Characteristics of Suspensions for Reconstitution Powder blend must be a uniform mixture of the appropriate concentration of each ingredient. During reconstitution, the powder blend must disperse quickly and completely in the aqueous vehicle. Reconstituted suspension must be easily re-dispersed and poured by the patient to provide accurate and uniform dose. Final product must have an acceptable appearance, odor and taste [25].

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