

THE PHARMA INNOVATION

Taste Masked Suspension

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Children are frequently failed to take medications properly because of unpleasant taste of medicament. Non-compliance can lead to worsening of diseased condition. Numbers of taste masking technologies have been used to address the problem of patient compliance. Use of sweeteners, amino acids and flavoring agents alone are often inadequate in masking the taste of highly bitter drugs. Coating is more efficient technology for aggressively bitter drugs even though coating imperfections, if present, reduce the efficiency of the technique. In Ion exchange resin (IER) method weak cation exchange or weak anion exchange resins are used for taste masking, depending on the nature of drug. The nature of the drug resin complex formed is such that the average pH of 6.7 and contain concentration of about 40meq/L in the saliva are not able to break the drug resin complex but it is weak enough to break down by hydrochloric acid present in the stomach. Thus the drug resin complex is absolutely tasteless with no after taste, and at the same time, its bioavailability is not affected. Children under the age of 8 are typically prescribed liquid medications because of smaller structure of a child's esophagus.

Keyword: Taste Masked Suspension, Taste masking

INTRODUCTION: Orally administered drugs are provided to the patient in many dosage forms, including solid forms such as capsules, tablets and liquid forms such as solutions, emulsions or suspensions. Pharmaceuticals administered in solid form are usually intended to be swallowed whole. Often the disagreeable taste of a drug does not need to be considered in formulating swallowable tablets or capsules. Because these dosage forms are in the mouth such a short time the pharmaceuticals taste can easily be masked with an exterior coating on the tablet. Children, older

persons, and many other persons including disabled or incapacitated patients often have trouble swallowing tablets or capsules. In these situations, it is desirable to provide the drug either in a chewable solid form or a liquid form. For many patients, including pediatric and geriatric patients, a liquid oral dosage form is preferable to a chewable dosage form. A liquid dosage is preferable for this class of patients because of the ease with which it may be swallowed. Additionally, patients may be more inclined to comply with their medication instruction if the dosages are easier to ingest. However, a common problem associated with liquid pharmaceutical dosage forms is the often disagreeable taste of a drug that may manifest itself when the drug is in a liquid dosage form.

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Many drugs are less soluble at higher or lower pH than at the pH value of the mouth, which is around 5.9. Some pharmaceutical compositions have utilized this concept and suspended the drug at a pH in which it remains insoluble. In this condition, the drug can be insufficiently solubilised to be available to taste if the equilibrium concentration is below the taste threshold. Taste masking of liquid formulation present a major challenge because the majority of pediatric preparations are syrups and suspensions. The bitter taste of vitamin B1 derivatives such as dicethimine was masked by formulating with menthol and or polyoxyethylene, polyoxypropylene for formulating oral liquids. Oral liquids containing Diclofenac and its salts were subjected to heat treatment in the presence of glycine, glyceric acid or salt thereof to mask the bitter taste and to prevent the irritation of the throat upon oral administration. Prolamine, applied as single coating in weight ratio 5% to 100% relative to active substance being coated result in the production of a liquid suspension which effectively masked the taste of orally administered drugs which are extremely bitter. Prolamine coating does not restrict the immediate bioavailability of the active substance Prolamine coating is effective in masking the taste of antibiotics, vitamins, dietary fibers, analgesic, enzymes, and hormones. Liquid suspension of at which pharmaceutically active ingredients remain substantially insoluble. Liquid composition comprising a pharmaceutically active medicament coated with a taste masking effective amount of polymer blend of dimethylaminoethyl methacrylate and neutral methacrylic acid ester and a cellulose ester in an aqueous vehicle. The liquid composition utilizes a reverse enteric coating, which is soluble in acid pH of the stomach generally about 1-4 but relatively insoluble at the non-acidic pH of the mouth. The coating provides the rapid release and absorption of the drug, which is generally desirable in case of liquid dosage forms microcapsules taste masked as a function of a polymer coating and the pH of suspended medium.

SUSPENSION¹⁻⁶

A pharmaceutical suspension is a coarse dispersion in which insoluble solid particles are dispersed in a liquid medium. The particles have diameters for the most part greater than 0.1 μ m and some of the particles are observed under the microscope to exhibit Brownian movement if the dispersion has a low viscosity⁴.

Suspensions contribute to pharmacy and medicine by supplying insoluble and often substances in a form for the application of dermatological materials to the skin and sometimes to the mucous membranes and for the parenteral administration of insoluble drugs. Therefore, pharmaceutical suspensions may be classified into three groups.

- a) Orally administered mixtures
- b) Externally applied lotions
- c) Injectable preparations

When formulated for use as pediatric drops, the concentration of suspended material is correspondingly greater. Antacid and radio opaque suspensions generally contain high concentration of dispersed solids. Externally applied suspensions for topical use are legion and are designed for dermatological, cosmetic and protective purposes. The concentrations of dispersed phase may exceed 20%. Parenteral suspensions contain from 0.5 to 30% of solid particles. Viscosity and particle size are significant factors since they affect the ease of injection and the drug in depot therapy.

Advantage^{3,4}

- Increase bioavailability
- Easy to manufacture
- Suitable for pediatric and geriatric patients
- Suspended insoluble medicaments are easy to swallow.

Disadvantage^{3,4}

- Preparation must be shaken prior to measuring a dose.

- Accuracy of dosage is less reliable than with solution.
- Crystal formation
- Breaking of suspension

Desirable qualities of an acceptable suspension^{3,4}

- The suspended material should not settle rapidly.
- The particles that do settle to the bottom of the container must not form a hard cake but should be readily redispersed into a uniform mixture when the container is shaken.
- The suspension must not be too viscous to pour freely from the bottle or to flow through a syringe needle.
- In the case of an external lotion, the product must be fluid enough to spread easily over the affected area and yet must not be so mobile that it runs off the surface to which it is applied.
- The suspension must dry quickly and provide an elastic protective film that will not rub off easily.
- It must have an acceptable color and odor and taste.

It is important that the characteristics of the dispersed phase are chosen with care so as to produce a suspension having optimum physical, chemical and pharmacological properties. Particle size distribution, specific surface area, inhibition of crystal growth and changes in polymorphic form are of special significance, and the formulator must ensure that these and other properties are not changed sufficiently during storage to adversely affect the performance of the suspension. Finally, it is desirable that the product contains readily obtainable ingredients that can be incorporated into the mixture with relative ease by the use of standard methods and equipments.⁵

TASTE MASKING

Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist¹¹.

Approaches to Unpleasant Taste Inhibition

(a) Addition of sweeteners, flavours & Amino acids

(1) Nutritive Sweeteners:

- Sucrose
- Glucose
- Dextrose
- Fructose

(2) Non Nutritive Sweeteners:

Table 1 Sweetness factors of Different Sweeteners	
Sweeteners	Sweetness factor, Sucrose=1
Aspartame	180-200
Sucralose	600
Acesulfame K	200
Neotame	7,000-13,000
Saccharin	300

(b) Taste Masking by Inclusion Complexation¹¹

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 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. This method is most suitable only for low dose drugs. Vander Waals forces are mainly

involved in inclusion complexes¹². β -cyclodextrin is the most widely used complexing agent for inclusion type complexes. It is a sweet, non-toxic, cyclic oligosaccharide obtained from starch¹. The strong bitter taste of carbetapentane citrate syrup was reduced to approximately 50% by preparing a 1:1 complex with cyclodextrin¹. Palatable ibuprofen solutions are prepared by forming a 1:11 to 1:15 inclusion complex with Ibuprofen and hydroxy propyl B-cyclodextrin, respectively¹³.

(c) Taste Masking by Ion-Exchange Resins¹²

Ion-exchange resins (IERS) are high molecular weight polymers with cationic and anionic functional groups (most common polymeric network is a copolymer of styrene and divinylbenzene). Drug can be bound to the resin by either repeated exposure of the resin to the drug in a chromatographic column or by prolonged contact of resin with the drug solution. Drugs are attached to the oppositely charged resin substrate, forming insoluble adsorbates or resinates through weak ionic bonding so that dissociation of the drug-resin complex does not occur under the salivary pH conditions. This suitably masks the unpleasant taste and odour of drugs. Drug release from the resin depends on the properties of the resin and the ionic environment within the GIT. Drug molecules attached to the resin are released by exchanging with appropriately charged ions in the GIT, followed by diffusion of free drug molecule out of the resins.

d) Taste Masking by Coating¹¹:

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

Agents used for coating

- Carbohydrates (Cellulose)
- Synthetic polymers (Eudragits etc)
- Proteins, Gelatine, and Prolamines (Zein)
- Zeolites

(e) Miscellaneous Taste masking Approaches¹¹

By Effervescent Agent

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have also 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(s) was formulated to supply the medicament(s) to the oral cavity for local application or for buccal absorption. It comprises a chewing gum base, an orally administrable medicament, a taste masking generator of carbon dioxide, and optionally a taste bud desensitising composition (e.g. oral anaesthetics such as benzocaine and spilanthal) and other non active material, such as sweeteners, flavouring components, and fillers¹⁴.

Microencapsulation

Microencapsulation involves coating of drug particles using a natural or synthetic polymer or was several techniques such as simple & complex coacervation, Solvent evaporation, Spray chilling Spray drying, annular jet, fluid-bed and spinning disk methods have been successfully used to prepare micro spheres. The unpleasant taste of clarithromycin was masked when the drug was encapsulated in combination of gelatine and acrylic resins such as Eudragit L-100, Eudragit S-100 & E-100.

Rheological Modifications¹¹

Increasing the viscosity with rheological modifiers 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 taste⁵. Gelatine and flavouring materials (chocolate flavour) mask the bitter taste of tannic acid by viscosity effects, when made into a jelly by cooling.

Salt Preparation¹¹

Adding alkaline metal bicarbonate such as sodium bicarbonate masks the unpleasant taste of water -soluble ibuprofen salts in aqueous solution. Penicillin prepared as N, N-di benzyl ethylenediamine diacetate salts or N, N-bis (dehydroabiety) ethylene diamine salts is tasteless¹¹.

Solid Dispersion Systems¹¹

Solid dispersions can be defined as the dispersion of one or more active ingredients in an inert solid carrier. Solid dispersion of drug with the help of polymers, sugar, or other suitable agents, is very useful for taste masking. The bitter taste of dimenhydrinate can be masked by preparing the solid dispersion of the drug with polyvinyl acetate phthalate¹¹.

Wax Embedding of Drug

Tastes masked by embedded granules of ephedrine HCl, Chlorpheniramine maleate, Diphenhydramine HCl were prepared in stearic acid & other waxes.

Group Alteration and Prodrug Approach

The alkyloxyalkyl carbonates of the clarithromycin 2' position have remarkably alleviated bitterness and improved bioavailability when administered orally. Tasteless prodrug of nalbuphine HCL, naltrexone, naloxone, oxymorphone HCL, butorphanol, and levallorphan were synthesized for buccal administration to improve bioavailability relative to that of oral dosing without the characteristic bitter taste¹⁶.

Liposomes¹¹

Incorporation of drug into liposomes prepared with egg phosphatidyl choline masked the bitter taste of antimalarial, Chloroquine phosphate in HEPES (N-2- hydroxyethylpiperzine-N'-2 ethane sulfonic acid) buffer at pH 7.2¹⁷.

Emulsion¹¹

The use of multiple emulsions for masking the bitter taste of chloroquine was investigated in o/w/o and w/o/w emulsion system.

Freeze Drying Process

This method is used to develop fast dissolving oral technologies such as Zydis and Lyoc technology. Zydis is a tablet shaped dosage form that spontaneously disintegrates in the mouth in seconds. This is due to high porosity produced by the freeze drying process. Various drugs have been taste-masked by Zydis technology. These are lorazepam (Wyeth), piroxicam (Pfizer), loperamide (Janssen), ondansetron (Glaxo Wellcome), rizatriptan (Merck), loratadine (Schering Plough), olanzapine (Eli Lilly), selegiline (Elan), ascopolamine/chlorpheniramine (Taisho)¹⁸.

Wet Spherical Agglomeration (WSA) Technique and Continuous Multipurpose Melt (CMT) Technology¹¹

A novel Microencapsulation process combined with the wet spherical agglomeration (WSA) technique was used to mask the bitter taste of enoxacin. The CMT method was developed for the continuous granulation and coating for pharmacologically active substances. It was concluded that this method could be successfully applied for taste masking of bitter drugs¹¹.

Table 3 Therapeutic Agents with Unpleasant Taste ¹⁹	
Class	Drugs
Antibiotics	Ampicillin, Cloxacillin, Pivampicillin, Azithromycin, Chloramphenicol, Erythromycin, Clarithromycin, Tetracycline, Doxycycline, Cefuroxime axetil, Cefedroxil, Norfloxacin, Ciprofloxacin HCl, Ofloxacin, Sparfloxacin, Roxithromycin
Antitussives	Caramiphen Edicylate, Codeine phosphate or sulphate, Dextromethorphan hydrobromide
Decongestants	Phenylepherin bitrate or tannate or hydrobromide or hydrochloride, Phenyl propenolamine HCl, Pseudo ephedrine
Laxatives	Diocetyl sodium sulphosuccinate
Expectorants	Guaifenesine, Potasium iodide or citrate, Potasium guaicolfonate, Terphin hydrate, Ethylmorphine
Antihistamines	Azatidenameliolate, Brompheniraminen maleate, Bromdipheniramine HCl, Chlorpheniramine maleate, Diphenhydramine HCl, Phenindamine tartrate, Pyrillamine maleate, Tripelenamine HCl, Cetrizine
NSAIDs	Fenbufen, Fenoprofen, Flubifronate, Ibuprofen, Meclofenamate sodoum, Mefenamic acid, Naproxen, Acetaminophen
Antiulcer	Ranitidine, Famotidine

Cerebral activator	Indeloxine
Antispasmodic	Dicyclomine, Itopride
Antimalarial	Chloroquine phosphate, Quinine hydrochloride
Antiemetics	Metoclopramide HCl,
Antiamoebic	Metronidazole, Sacnidazole

CONCLUSION

Taste masked suspension of a simple rapid and cost effective method like complexation with ion exchange resin for taste masking that may be acceptable to the industries. Sometimes, the taste of the drug in the dosage form may be overpowered by adding sweeteners or flavoring agents to the liquid dosage. These agents mask the bitter or unpleasant taste of drugs. However, if the drug is especially bitter or foul tasting, as is the case for many antibiotics, analgesics and CNS drugs, coating of the active ingredient particles or forming other controlled-dissolution dosage forms may be required. This allows time for all of the particles to be swallowed before the threshold concentration is reached in the mouth and the taste is perceived. The general requirement in taste-masking is to delay the release of the drug sufficiently to eliminate immediate taste, but also to delay the release from particles trapped between the teeth, in the gum line and so on for a total of perhaps five to 10 minutes, after which they are largely carried away by saliva flow. Release of the drug should be kept to a minimum over this period of time .

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