Review Article

RECENT TRENDS IN TASTE MASKING OF BITTER DRUGS

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ABSTRACT

Taste masking of liquid formulation present a major challenge because the majority of pediatric preparations are syrups and suspensions. 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. In addition to oral drug delivery, taste masked drug delivery research is gaining importance and commercial success for the quality of treatment provided to suffering patients, especially children. As evidenced by the number of patents and technological developments we made an attempt that an ideal taste masking is widely accepted in the development of more palatable and acceptable dosage forms which not only lead to better patient compliance but with an ultimate clinical output. **Keywords**-Taste masking, Bitterness;Complexation,Patient compliance.

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 swallow able 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

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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. 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. Thev present a maior challenge in taste masking because the majority of pediatric preparations are syrups and suspensions although, the
 Table 1: Flavoring agents for taste
masking

Basic Taste	Masking agents
Sweet	Vanilla, Bubble gum, Grapefruit
Acid	Lemon, Lime, Orange, Cherry, Grapefruit
Metallic	Grape, Marsh, Mellow, Gurana, Berries, Mints
Bitter	Liquorice, Coffee, Chocolate, Mint, Grapefruit,

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aforementioned methodologies havealso had been used for improving liquid taste and few patents in this area are worth mentioning. Taste is an important factor in the development of dosage form. Nevertheless it is that arena of product development that has been overlooked and undermined for its importance.

TASTE MASKING¹⁻⁹

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

Cherry, Peach, Raspberry, Orange, Lemon, Lime.

(2) Non Nutritive Sweeteners:

Table 1 Sweetness factors of DifferentSweeteners			
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 Complexation¹⁰

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 Walls forces are mainly involved in inclusion $complexes^{12}$. β -cvclodextrin 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 1:1 complex with а cyclodextrin¹. Palatable ibuprofen solutions are prepared by forming a 1:11 inclusion complex to 1.15 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 divinylbezene.)Drug can be bound to the resin by either repeated exposure of the resin to the drug in a chromate graphic 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

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also been employed for use as taste masking agents for dosage forms that are not dissolved in water prior to administration. А chewing gum composition of bitter medicaments(s) was formulated to supply the medicament(s) to the oral cavity for local application or for buccal absorption. It comprises a chewing gum administrable base. an orally medicament, a taste masking generator of carbon dioxide, and optionally a taste bud desensitising composition (e.g. oral anaesthetics such as benzocaine and spilanthol) 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, fluidbed and spinning disk methods have been successfully used to prepare micro The unpleasant taste of spheres 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 Preparation**¹¹

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 (deyhdroabiety) 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, butorphanonol, 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

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liposomes prepared with egg phosphatidyl choline masked the bitter taste of antimalarial. Chloroquine HEPES (N-2phosphate in hydroxyethylpiperzine-N'-2 ethane sulfonic acid) buffer at pH 7.2^{17} .

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 bv the freeze drving process.Various drugs have been tastemasked by Zydis technology. These are lorazepam (Wyeth), piroxicam (Pfizer), loperamide (Janssen), ondansetron (Glaxo Wellcome), rizatriptan (Merck), loratadine (Schering Plough), olanzapine selegiline (Eli Lilly), (Elan). ascopolamine/chlorpheniramine $(Taisho)^{18}$.

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

Wet Spherical Agglomeration (WSA)TechniqueandContinuousMultipurposeMeltTechnology11

A novel Microencapsulation process combined with the wet spherical agglomeration (WSA) technique was

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another. Nowadays, sensory analysis employs objective or analytical methods and subjective or hedonic method ²⁴ (Table 3).

al,⁴⁷ invented Soutakagi, et а 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 de 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 recorded are immediately assigned values and between 0-3¹⁹

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, Dextromethromethorphan hydrobromide	
Decongestants	Phenylepherin bititrate or tannate or hydrobromide or hydrochloride, Phenyl propenolamine HCl, Pseudo ephedrine	
Laxatives	Dioctyl sodium sulphosuccinate	
Expectorants	Guaifenesine, Potasium iodide or citrate, Potasium guaicolfonate, Terphin hydrate, Ethylmorphine	
Antihistamines	Azatidenameliate, 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	

Subjective Method	Objective Methods	
Preference Test	Difference Test	
Paired Testing	Paired Difference Test	
Triangle Testing	Triangle Difference Test	
	Duo trio Test	
	Ranking Test	
	Analytical Test	
Hedonic Scale	Flavor Profile	
fiedome scale	Time Intensity Test	
	Single attribute test	
	Dilution Profile	
	Statistical Test	

Table 4: Evaluation of Taste masking

CONCLUSION

Taste masked suspension of a simple rapid and cost effective method like complexation with ion exchange resin for taste masking that may 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

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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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