WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 14, 172-188. Review Article ISSN 2277– 7105

REVIEW ON TASTE MASKING OF BITTER DRUGS BY USING ION EXCHANGE RESIN METHOD.

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Article Received on
10 September 2020,

Revised on 30 Sept. 2020,
Accepted on 20 October 2020

DOI: 10.20959/wjpr202014-19011

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ABSTRACT

The masking of bitter drugs is now a days top most priority of pharmaceutical companies in order to improve the poor taste and palatability. The various organoleptic properties such as taste, smell, texture, also these are important factor in development of oral dosage form. The taste is major factor of patient compliance and product quality. Acceptability of any dosage form mainly depends over its taste i.e. mouth feel. Drug molecules interact with taste receptor on the tongue to give bitter, sweet or other taste sensation of taste by single transduction of receptor organs.

KEYWORDS: Taste, taste bud, taste masking, ion exchange resin, taste masking technique.

INTRODUCTION

Taste

Definition of taste

Taste is ability to respond to dissolved molecules and ion called tastants.it is defined the sense that distinguishes sweet, sour, salty, and bitter qualities of dissolved substances in contact with the taste buds on the tongue and this sense in the combination of smell and touch together receive a sensation of a substance in a mouth.

Anatomy of taste bud

The taste and smell are collectively known as chemical senses. Tongue is a versatile and muscular organ which is related to taste sensation. The four common taste are sweet, sour, bitter, and salty. The taste are important factors in patient compliance. Taste transduction involves the interaction of molecule with taste receptor cells, which reside in specific structures called as Taste buds. avoid such a problem, many techniques have been developed

to mask the bitter taste of drug these are prodrug approach, ion exchange resin, microencapsulation, granulations inclusion complexes.

Physiology of taste

The taste buds are onion -shaped structures containing between 50 to 100 cells. Chemicals forms food or ingested medicine are dissolved by the saliva and enter via the taste pore. There are interact with surface protein known as taste receptors. Or with pore protein s known as channels. These interactions cause electrical changes within the taste cells that triggers them to send chemical signals that translate into neurotransmission to the brain.

Type of tastes

- Bitter -Allows sensing of diverse natural toxins
- Salty -Allows modulation diet for electrolyte balance
- Sour -Typically the taste ae acids
- Sweet -Usually indicates energy rich nutrients.

Taste Masking of Bitter Pharmaceutical Agents

Oral pharmaceutical with a perceived bitter taste may include chewable tablets, capsule suspension, lozenges, mouthwashes, dentifrices, syrups, and ingestible ointment. However, there are certain methods for reduction of bitterness thus resulting in improve taste by masked with certain ingredient such as flavors, sweeteners, gelatin, gelatinized starch, chitosan, cyclodextrin, lecithin, and lecithin like substance, surfactants, salts and ion exchange resin. Taste is one of the most important parameters governing patient compliance. Undesirable taste is one of the important formulation problems that are encountered with many drugs. Administration of bitter drugs usually with acceptable level of palatability is a key issue for healthcare provide especially for the pediatric patients.

Importance of Taste Masking

Organoleptic characteristic of pharmaceutical product i.e. mainly appearance odor and taste are essential factor in assessing the patient acceptability thereby commercial success in market.

Undesirable taste is main formulation problem because more than 50% pharmaceutical active ingredients having bitter taste so for the pediatric and geriatric patient compliance it required to masked the taste by suitable technique.

Taste masking of bitter formulation is done by various technique but it is importance to find out the method that can mask the taste and also ensure the dissolution of the drug. Administration of the bitter drug orally with acceptable level of palatability is key issue for health care providers especially in case of pediatric patient. In fact taste masking has becomes potential tool to improve patient compliance and commercial success of product.

Various taste masking techniques available in oral pharmaceutical formulations

A suitable taste masking technique can powerfully impact both, quality of taste masking and process effectiveness.

Approaches to overcome bad taste

Two approaches are commonly utilized to overcome bad taste of the drug.

1. Reduction of drug solubility in saliva, where a balance between reduced solubility and bioavailability must be achieved.
2. After the ability of the drug to interact with taste receptors.

There are many techniques developed for taste masking pf bitter pharmaceuticals. These are as follows

Methods of Taste Masking

- Addition of flavor and sweeteners
- Coating
- Microencapsulation
- Ion exchange resin
- Inclusion complexation
- Granulation
- Adsorption
- Prodrug approach
- Bitterness inhibiters
- Liposomes and Multiple emulsions
- Gel formulations

Taste masking technology induces two aspects

- Selection of suitable taste masking substances such as polymers, sweeteners, flavors, amino acids etc.
- Selection of suitable taste masking technique.

Ideal properties of taste Masking process

1. Covered least number of equipment's processing steps.
2. Required minimum number of excipients for an optimum formulation.
3. No undesirable effect on drug bioavailability.
4. Price effectiveness.
5. Rapid and easy to prepare.
6. Required excipient that are economical and easily available.
7. Can be carried out at room temperature.

A) Addition of flavors and sweeteners

Flavoring refers to a complex effect of a taste, odor and feeling factor so as to make preparation more palatable. the selection of flavors depends on the taste that is to be mask. Sweeteners are commonly used in the taste masking of drugs. These can be mixed with bitter drugs so as to improve the taste of the core material. The taste masking can be achieved by using amino acids like glycine, alanine, leucine, etc. Sweeteners like sucrose and its derivatives, sodium saccharin, sativoside, aspartame, monosodium glycyrrhizinate and flavoring agents like lemon water, vanillin, citrus etc. Sweeteners ae used in the combination with sugar alcohols like lactitol, maltitol and sorbitol to reduce their after tasted perception.

B) Taste masking by coating

Coating is one of the commonly used and efficient method used in taste masking technologies. The coating material is divided into three types lipids, polymers, and sugars. The coating acts as a physical barrier to the drug particles, thereby minimizing interaction between the drug and taste buds. Hydrophobic polymers, Lipid sweeteners, and Hydrophilic polymers as used as coating materials. either alone or in combination, as a single or multi-layer coat. Polymeric film coating is the most widely used industrial technique for taste masking. Various film former likes povidone, acrylate, Hydroxypropyl cellulose, Hydroxypropyl methylcellulose etc. Can be used for coating. Film former like povidone gives clear, glossy and hard film while acrylates gives transparent and elastic film.

Table 1: List of different type of polymers with examples.

Type of polymer	Examples
Water soluble polymers	Polyvinyl pyrrolidone, hydroxy ethyl cellulose
Water insoluble polymer	Crossprovidone, ethyl cellulose, cross cramellose
pH dependent water insoluble polymers	Polycarbophil, polyacrylic acid
pH independent water insoluble polymer	Polyvinyl acetate, cellulose ester, cellulose ethers

Reverse enteric polymers	Vinyl pyridine, hydroxy ethyl methacrylate, eudragit E 100
Enteric polymers	Acrylic acid esters, phthalate, hydroxy phthalates
Spacing layer polymers	Ethyl cellulose: PVP

C) Microencapsulation

Microencapsulation is a process by which very tiny droplets of solid material are surrounded by with a polymeric material. In this method bitter drugs are first encapsulated to give free flowing micro capsules which are then blended with excipients and compressed into tablet. The coating agents are used are gelatin, povidone HPMC, ethyl cellulose, wax, acrylics and shellac. Diphenhydramine (DPH) was incubated with starch at different temperatures (35 to 55ºc) for different time periods (1 ++to 4 hours) diphenhydramine loaded starch particles were then dried and results revealed taste masking of parent drugs. The process can be done by using techniques such as coacervation -phase.

D) Ion Exchange Resin

Ion exchange resins are high molecular weight polymers with cationic and anionic functional groups. They can exchange their mobile ions of equal charge with surrounding medium. Drug are attached to the resin substrate to form the insoluble resinates though weak ionic bonds so that the drug resin complex will not be dissociated under normal salivary pH conditions, this suitably masks the unpleasant taste and odor of drugs.

Chemistry

An ion exchange resin is a polymer with electrically charged sites at which one ion replace another. Natural soils contain solids with charged sites that exchange ion and certain minerals called zeolites are good exchangers. The cell wall and cell membrane also carrying a charge so ion exchange also takes place in that.

Synthetic ion exchange resin having porous beads with considerable external pore surface at which ion can attach. The resin is prepared in spherical beads shape and having diameter 0.5 to 1.0mm diameter. These appears solid even under microscope but on a molecular scale the structure is open. When greater the surface area greater is the absorption. When a substance is adsorbed to a resin, no ion is liberated. There are numerous functional groups that having charge, only few are commonly used for man-made ion exchange resin.

These are

- COOH, which is weakly ionized to –COO-.
- SO_3H, which is strongly ionized to $–SO_3$-.
- NH_2, which is weakly attracts proton to form NH_3+.
- Secondary and tertiary amines that also attract protons weakly.
- NR_3+ which has strong and permanent charge. (R for organic group).

Classification

Ion exchange resins are classified into two main categories:

1) Cationic exchange resin

- Strong acid
- Weak acid

2) Anionic exchange resin

- Strong base
- Weak base

1. Cation Exchange Resin

These are prepared by the copolymerization of styrene and divinyl benzene and have sulphonic group (-SO_3H) introduced into most of the benzene rings. The mechanism of cation exchange process: -

Resin—ex++ C+ → Resin—C+ +ex+

Where, resin- indicate a polymer with SO_3- sites available for binding with exchangeable cation (ex+), and C+ indicate a cation in the surrounding solution getting exchanged.

Cation exchange resin classified as: -

A. Strong Acid Cation Exchange Resins

These resins are highly ionized in both the acid (R-SO_3H) and salt (R-SO_3Na) form of the sulfonic acid group (-SO_3H). These can convert a metal salt to the corresponding acid by the reaction:

2(R-SO_3H)+ → $NiCl_2$ (R-SO_4)Ni+ 2HCl

The hydrogen and sodium forms of strong acid resins are highly dissociated, and the exchangeable Na+ and H+ are readily available for exchange over the entire pH range. Consequently, the exchange capacity of strong acid resins is independent of the solution pH. The resin would be used in the hydrogen form for complete deionization; they are used in the sodium form for water softening (calcium and magnesium removal). After exhaustion, the resin is converted back to the hydrogen form (regenerated) by contact with a strong acid solution, or the resin can be convened to the sodium form with a sodium chloride solution. For the above reaction, hydrochloric acid (HCl) regeneration would result in a concentrated nickel chloride ($NiCl_2$) solution.

B. Weak Acid Cation Exchange Resins

These resins are behaving similarly to the weak organic acids that are weakly dissociated. In a weak acid resin, the ionizable group is a carboxylic acid (COOH) as opposed to the sulfonic acid group (SO3H) used in strong acid reins. The degree of dissociation of a weak acid resin is strongly influenced by the solution pH. Consequently, resin capacity depends in part on the solution pH. A typical weak acid resin has limited capacity below a pH of 6.0, making it unsuitable for deionizing acidic metal finishing wastewater.

2. Anion exchange resin

These having exchangeable ion are negatively charged. These are firstly prepared by the chloromethylation the benzene rings of styrene-divinyl benzene copolymer to attach CH2Cl groups then causing to react with the tertiary amines such as triethylamine. The mechanism of anion exchange process:

Resin+- ex-+ A- $\longrightarrow$ Resin+ -A- +ex-

Anion exchange resin can be classified as: -

a) Strong Base Anion Exchange Resins

These resins are highly ionized and used over entire pH range. These resins are used in hydroxide form for deionization. These are reacted with anions in solution a can convert an acid solution and can convert an acid solution to pure water:

$R\text{-}NH_3OH + HCl \longrightarrow R\text{-}NH_3Cl + HOH$

Regeneration with concentrated sodium hydroxide (NaOH) converts the exhausted resin to the OH form.

B) Weak Base Anion Exchange Resins

These resins are like weak acid resins in that the degree of ionization is strongly influenced by pH. These having exchange capacity above a pH of 7.0. The weak resin does not have OH ion form as does the strong base resin.

$R\text{-}NH_2 + HCl \longrightarrow R\text{-}NH_3Cl$

Kinetics of ion exchange process

The ion exchange is basically a diffusion process and also related to chemical reaction kinetics.it can be described as a series of consecutive reaction and mass transfer processes

The steps are as follows –

i) Film diffusion- the exchangeable counter ion must diffuse through the adherent external solution to the surface of the ion- exchange.

Preparation of resinate

Preparation of resinate done through two methods namely batch process and column process

1. Batch process

In this method, the ion exchange is resin added to water and make a slurry. Then accurate weighed amount of drug is then added to this slurry which is followed by stirring to prepared the complex, after the formation of the complex, it is washed and water is dried.

2. Column process

In a typical column procedure, the resin is slurred in water and added to a column and backwashed with water to eliminate air pockets and distribute the beds. Acid (0.1N HCL) is added to convert the acid cycle, followed by washing with water. The cake is then removed from the column, subjected to vacuum filtration and finally dried in an oven. An analogous procedure can be used to absorb a carboxylate drug on ion exchange resin, using NAOH to convert the resin to basic cycle.

Factor affecting ion exchange resin complexation

I particle size and form-

The rate of ion exchange reaction is depending on the size of the resin particles. The reduction of the resin particles results in decreased time required for the reaction to reach the equilibrium with the surrounding medium.

II porosity and swelling

Porosity affects the ability of ions to penetrate into resin matrix and thus positive efficiency of complexation. The amount of cross-linking substance used in polymerization method determines the porosity of resin. The amount of resin is directly proportional to the number of hydrophilic functional group attached to the polymer matrix, and is inversely proportional it the degree of DVB cross linking present in the resin.

III cross linking

The cross-linking percentage affects the physical structure of the resin particles. Resin having low degree of cross linking can take up large quantity of water and thus swell into a soft gelatinous structure. Cross linking also affects the loading efficiency of resin by affecting its porosity and swelling properties.

IV Exchange capacity

The number of ionic sites per unit weight or volume (meg/gm or meg/ml). The exchange capacities determine the amount of drug that can be absorbed on a resin hence the potency of complex.

V Mixing time

If increase in the mixing time increase the swelling of resin which results in increased drug loading.

VI Effect of temperature

High temperature causes swelling of resin. Cation exchange resin doesn't get significantly affected by temperature changes unlike anion exchanger.

VII pKa

The pka value of resin is having significant influence on the rate at which the drug is released from the resinate in the gastric fluids. The extents of dissociation and complexation with the resin is also depends on pka of the drug. If the pH is higher than pka of the drug, the drug remains in unionized form resulting in decreased complexation. At certain pH, both the drug and resin are ionized in sufficient quantity so maximum resinate formation.

VIII Purity and toxicity

Resins are not absorbed by body tissue and are safe for human consumption. Careful purification of resin is required to remove any toxic impurities in a test conducted for

toxicological tolerance, the resins were found to be physiologically inert and non-toxic at recommended dosage.

E) Inclusion complexes

Inclusion complex is a 'host-guest' relationship in which the host is complexing agent and guest is the active moiety. The complexing agent is capable of masking bitter taste either by decreasing it's to taste buds. Vander Waal forces are mainly involved in inclusion complexes. B-cyclodextrin is widely used complexing for taste masking of drugs due to its sweet taste and is not toxic in nature.

F) Granulation

Taste masking of a bitter taste drug can be masked by granulation process. Granulation is major and a common process in tablet production. In this approach, saliva insoluble polymers are used as binding agents in the tablet preparation. As these polymers are insoluble in saliva, thus the bitter taste of the drug can be masked. The taste masked granules can also be formulated as chewable tablet and rapidly disintegrating tablets.

G) Adsorption

Adsorption of bitter drug can be considered as less saliva soluble version of that drug. In this technique, adsorbates of the bitter drugs are prepared by adsorption process. This process involves the adsorption process. This process involves the adsorption of the drug solution using insoluble materials like saliva gel, bentonite, vee gum etc. the adsorbate (resultant powder) is dried and used for the formulation of final dosage forms.

H) Prodrug approach

Prodrug are therapeutic agents that are initially inactive but on biotransformation liberate active metabolite by which the therapeutic efficacy is obtained.

Molecular geometry of the substrate is important for the taste receptors adsorption reaction i.e., mechanism of taste. Hence if any alteration is done in molecular geometry, it lowers the adsorption rate constant. Thus, taste masking can be achieved through prodrug approach. Other advantages of prodrugs include change in aqueous solubility, increase lipophilicity, improved absorption, less site effects and change in membrane permeability etc.

Table 2: Examples of drugs taste masked by ion exchange resins.

Drug	Resin used	Reference
Azithromycin	Indion 234, Indion 204	81, 84,93, 102
Ambroxol hydrochloride	Indion 204, Indion 234	89,97
Betahistine hydrochloride	Tulsion 344	93, 81
Ciprofloxacin	Indion 234	84,93,103,107,108
Cefuroxime axetile	Indion 214, Indion 234	93
Chloroquine phosphate	Doshion P 544, Kyron T 114	84,93,103,105
Cetirizine hydrochloride	Tulsion 399, Tulsion 335	93,105
Clarithromycin	Tulsion 335	81
Dicyclomine hydrochloride	Indion 234	81, 84, 93, 103, 113
Doxylamine succinate	Indion 204, Indion 234	84,116
Dextroamphetamine	Tulsion	93
Erythromycin	Indion 204, Kyron T 114	81,84
Etoricoxib	Indion 204, Indion 234	118,119
Fexofenadine	Doshion P 547	103, 114, 117
Fluoroquinolone	Tulsion 339, Indion 214	112,117
Itopride HCL	Doshion P542, Tulsion 344,	93,103
Levofloxacin	Tulsion 335	81,103
Levamisole	Amberlite IRP -69	103, 114, 123
Metronidazole	Kyron T 114, Indion 234	81,84,93,113
Metoclopramide HCL	Indion 204	91, 105
Metronidazole benzoate	Kyron T 104, Indion 234	81,84,105
Ondansetron HCL	Indion 204, Indion 414	128,129, 130
Ofloxacin	Tulsion T 335, Kyron T 114 Indion 204	84,93,106
Pseudoephedrine	Tulsion T 344, Indion 244	133
Quinine sulphate	Indion 234	84,134,135
Roxithromycin	Indion 214	81,84,93, 106,108
Ranitidine Hcl	Indion 234	136
Risperidone	Amberlite IPR 64	137,138,139
Rapimelt	Kyron T 134	137,138
Tramadol Hcl	Tulsion 335	143
Tinidazole	Kyron T 114 Kyron T 134, Indion 214	146,147,18
Zolpidem	Tulsion 335	113,117

I) Bitterness inhibiters

The development of a specific universal inhibitors for bitter taste has been widely required in the field of taste physiology. One difficulty in discovery of universal inhibiter for bitter taste is that a substance that inhibits bitterness of one compound will not influence the bitterness of a second because many different classes of compound impact bitterness. Bitter substances are commonly hydrophobic in nature hence lipoprotein (PA-LG) composed of phosphatidic acid and ß-lacto globulin can mask the target site for bitter substances of taste receptor membrane without affecting responses to salt, acids, sugars, or sweet amino acids.

J) Liposomes and multiple emulsions

Liposomes are carrier molecules comprising several layers of lipids, in which the bitter drug is entrapped layers of lipids, in which the bitter drug is entrapped within the lipid molecule. oils, surfactants, polyalcohol's and lipids effectively increase the viscosity in the mouth due to which the time of contact between the bitter drug and taste receptors is decrease, thus improving the overall taste masking efficiency.

Inhibition of bitterness of drugs by phospholipids such as lecithin etc. has been reported. The bitterness of chloroquine phosphate in HEPES buffer (pH 7.2) is masked by incorporation into a liposomal formulation prepared with egg phosphatidyl choline.

Multiple emulsions are also a good approach for taste masking of bitter drugs. Thus, is achieved by dissolving the drug moiety in the inner aqueous phase of w/o/w emulsion with good self-life stability. o/w/o emulsion is a type of multiple emulsion in which water globules, conversely w/o/w emulsion are those in which internal and external aqueous phases are separated by the oil. Both types of multiple emulsions are prepared for chloroquine sulphate and reported to be partially effective in masking the bitterness of the drug.

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