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Review Article

TASTE MASKING: BY ION EXCHANGE COMPLEXATION TECHNIQUE

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ABSTRACT

Organoleptic properties such as taste, smell and texture are also the important factors in development of oral dosage forms. Taste is one of the major factors which affect the patient compliance and product quality. Acceptability of any drug dosage form mainly depends over its taste i.e. mouth feel .drug molecule interacts with taste receptor on the tongue to give bitter, sweet or other taste sensation, when they dissolve in saliva. This sensation of taste is the result of signal transduction from the receptor organs for taste, commonly known as taste buds. Now a days most of the potent drugs that may be cardiac, analgesics, anti-inflammatory, antitubercular, anthalmentics , antibacterial ,anticoagulants, anti-epileptics, antimalarials, anti neoplastics, anti-thyroids, antiprotozoal, diuretics,histamine receptor antagonists, nutritional agents, opioids analgesics, oral vaccines and sex hormones , most of them are bitter in taste. So it becomes necessary to develop such a dosage for that must be acceptable in taste to patient especially in case of children or geriatrics. Masking of bitter and obnoxious taste of drugs in paediatric and geriatric formulations is a challenge to the pharmacist to ensure patient compliance and product value where the process and formulation should be economic, rapid and easy, involve least number of equipment, processing steps and minimum number of excipients without adverse effect on drug bioavailability.

Keywords*: taste and taste buds, taste masking, ion exchange complexation, taste masking techniques*

INTRODUCTION

Oral drug delivery refers to approaches, formulations, technologies, and systems for transporting pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect. Drug delivery technologies modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance. [1]

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More than 50% of pharmaceutical products are orally administered but undesirable taste is one of the important formulation problems that are encountered with such oral products. Taste of the product is one of important parameter governing patient compliance. Hence taste masking of oral pharmaceuticals has become important tool to improve patient compliance and the quality of treatment in pediatrics. Hence formulation of taste masked products is challenge to the pharmacist. [8]

Consumer acceptability certainly affects commercial success of the product in the market. Various techniques are available to mask the bitter taste or to improve the taste such as by using polymeric coatings, complexation with cyclodextrin, ion

exchange resins and use of various excipients such as sweetners, flavours etc.[8]

Oral Dosage Forms

Among different choices, oral dosage forms are usually the most convenient choice. As known worldwide, taking a medicine via oral route is one of the best options. As it is the simplest and easiest way for any patient to take a medication. For many advantages

Advantages

- Appropriate for any patient, whatever the age is
- The most natural and easiest route of administration
- Includes a big variety of dosage forms
- Economical and safe to the patient
- No nursing is required, which means the patient can take it with no help
- Toxicity is delayed due to the late onset of action which permits easier recovery than in case of other dosage forms

Disadvantages

- Delayed onset of action because absorption takes time
- Not suitable in emergency and for unconscious patients
- Not convenient for a patient with a gastrointestinal disorder such as diarrhea, constipation, ulceration, and hyperacidity in stomach
- Sometimes, the medication itself is the cause of such problems in the GIT like aspirin and many NSAIDs which may lead to ulcers in stomach upon recurrent usage on the long run
- Not convenient if the patient suffers mal-absorption syndrome in which absorption through small intestine is not ensured
- Not adequate for medications liable to inactivation or destruction in the GIT. E.g. insulin is a protein, if taken orally, it's digested in the stomach like the protein present in food such as meat and fish
- Not a good choice in case of uncooperative patients as children and infants
- Not appropriate if the patient suffers chronic vomiting

Types of oral dosage forms

Tablets

They are the most renowned oral dosage form among them all. There are various shapes, sizes and colors of tablets. They are present in different forms such as the flash, the chewable, or the simple one you swallow.

Capsules

Cylindrical shells inside which the medication is filled as granules, powders, pellets, or a mix of two or three of them. After taking the capsule, it breaks and drug is released in the appropriate time according to the kind of medication and design of the capsule.

Oral suspensions

The drug is mixed with a liquid, but without being dissolved. The drug particles are suspended in the liquid. The suspension should be shaken before use to diffuse the drug particles uniformly in the liquid. Hence, optimum doses are guaranteed.

Emulsions

Specific type of liquids administered orally. They are mainly either oil in water (O/W) or water in oil (W/O) emulsions. Water is inside oil or vice versa.

Lozenges

Small tablets intended to be dissolved inside the mouth slowly. They are used for achieving local effect as soothing and

purging the throat. Sometimes they are used to relieve cough.[9]

Reason

Oral administration is the most popular route due to ease of manufacturing, pain avoidance, accurate dosing, stability and ease of administration. However, pediatric patients find it difficult to swallow solid dosage forms like tablets and do not take their medication as prescribed. This results in high incidence of patient non-compliance and ineffective therapy. In market there are lots of formulations is available but it's bitter taste leads to poor patient compliance. Moreover, liquid preparation and suspension are available but they lack in stability. So, dispersible tablet or oral films are formulated to overcome above problem and taste masking approach was undertaken to mask the bitter taste of the drug. So, this formulation seems to be promising formulation for Pediatrics.

OVERVIEW OF TASTE MASKING

Taste is the ability to detect the flavor of substances like food, drugs etc. Taste is now became an important factor governing the patient compliance. It gained importance as the most of the drugs are administered through oral route. Administration of unpalatable drugs is hamperedby their unpleasant taste particularly in case of pediatric and geriatrics. [5]

Administration of an orally having bitter and obnoxious tastes with acceptable level of palatability is a challenge to the pharmacist in the present world, especially in pediatric and geriatric formulation. Thus taste masking in the present day pharmaceutical industry has become a potential tool to improve patient compliance and commercial success of the product.

Definition

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

Taste buds

Taste buds contain the receptors for taste. They are located around the small structures on the upper surface of the tongue, softpalate, upper esophagus, the cheek, epiglottis, which are called papillae. These structures are involved in detecting the five (known) elements of taste perception: salty, sour, bitter, sweet, and umami. In reality these tastes can be detected by any area of the tongue. Taste buds detect chemicals dissolved in saliva from food in the mouth and throat. Then, these taste buds send their sensory information through neurons to the gustatory center of the brain. Via small openings in the tongue epithelium, called taste pores, parts of the food dissolved in saliva come into contact with taste receptors. These are located on top of the taste receptor cells that constitute the taste buds. The taste receptor cells send information detected by clusters of various receptors and ion channels to the gustatory areas of the brain via the seventh, ninth and tenth cranial nerves. [10]

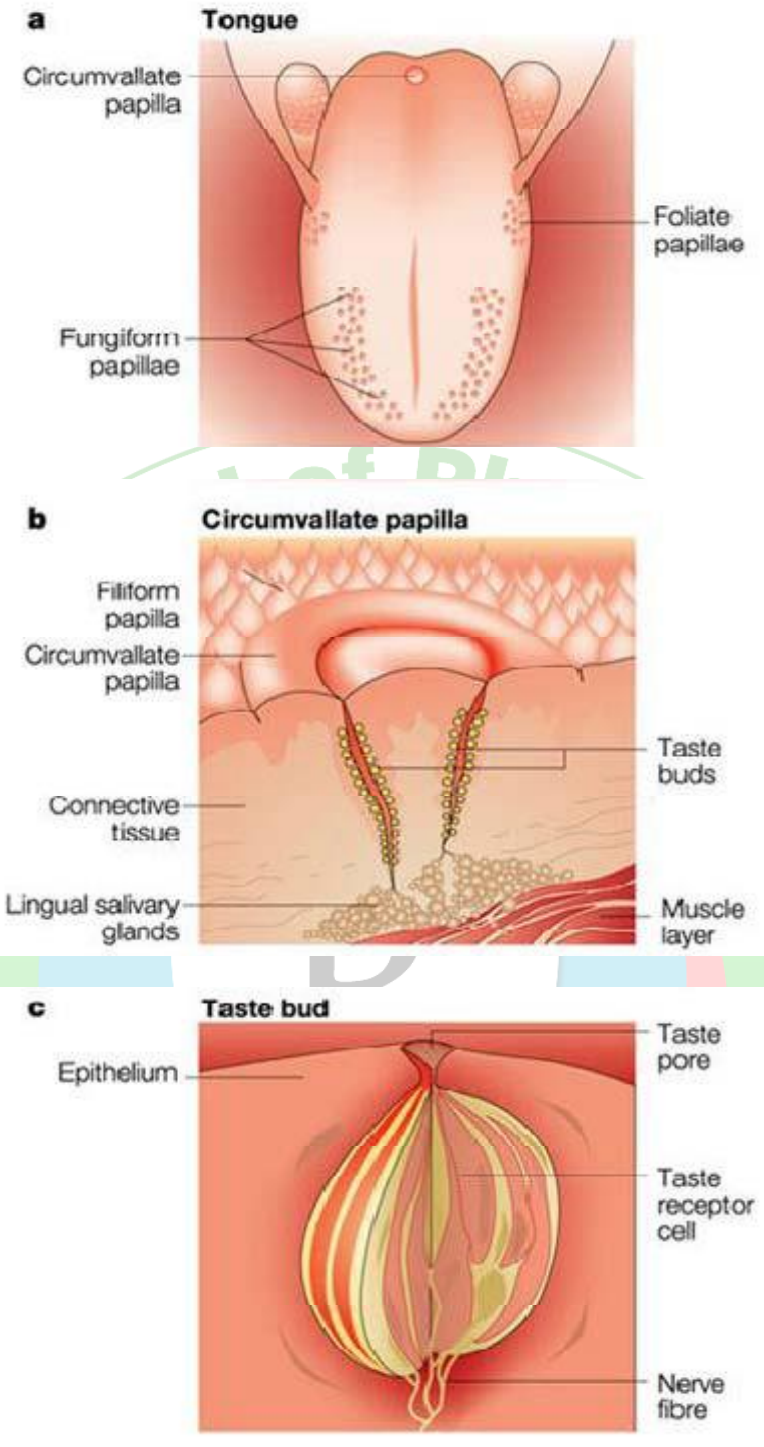

Fig. 1: Structure of taste bud

There are five known tastes that are detected by taste buds: sweet, salty, sour, bitter, and umami. Although these tastes are detected by all taste buds, some regions of the tongue have a slightly higher sensitivity to some tastes than others.

Sweet taste

They are found on the tip of the tongue. It is created by carbohydrates such as sucrose and fructose, as well as artificial sweeteners such as aspartame and saccharine.

Salty taste

They are located on the edge and upper front portion of the tongue. It is generally created by salts containing sodium ions, such as sodium chloride (table salt) and sodium bicarbonate (baking soda). Salts containing potassium, lithium, and other alkali metal ions also produce a mildly salty flavor.

Sour taste

They occur at sides of the tongue and are stimulated mainly by acids.Acidic compounds, such as citric acid and vinegar, produce sour flavors.

Bitter taste

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That is located toward the back of the tongue. This flavors are produced by a variety of organic compounds and are generally considered an undesirable or unpalatable flavor. Many toxic chemicals produced by poisonous plants have a bitter taste, thus leading to the negative reaction to bitter foods.

Umami, or savoriness

It is the most recently discovered taste, found in foods that have a "meaty" taste due to the presence of the chemical glutamate. Meat, cheese, mushrooms, and the chemical monosodium glutamate (MSG) all contain glutamate

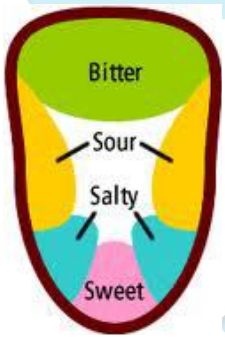


Fig. 2: Location of taste

Working of taste buds

Soluble chemicals present in food are dissolved by saliva very quickly after being placed in the mouth. These dissolved chemicals, known as tastants, spread throughout the mouth, enter the valleys between the papillae of the tongue, and pass into the taste pores. Taste hairs extending into the taste pores detect these tastants and stimulate their connected taste receptor cells to pass signals on to the sensory neurons in the tissue deep to the taste bud. These signals are passed on to the gustatory region of the brain where the sense of taste is interpreted. Taste buds works by transmitting information about different kind of taste to brain via nerve fibers.

The receptor cells are of two types functionally. One is ion channel type receptor, is a transmembrane protein which allows the ions that give rise to sensation of salt and sour. These ionic interactions cause electrical change within taste cells that trigger neurons to send chemical signals (that translate into neurotransmission) to the brain. These cells have a net negative charge in normal state. Tastants alter this state by using various means to increase positive ion concentration within the taste cell. This depolarization causes the cell to release neurotransmitters, there by relaying the

electrical messages to brain. The other is a surface protein receptor, allows binding of tastants (molecules having sense of taste) which give the sensation of sweet, bitter and umami. In case of bitter taste, stimuli acts by binding to G-Protein coupled receptor. Further leads to the splitting of G-Protein sub units and activation of the nearby enzyme present, finally resulting the release of secondary messengers. The secondary messengers initiate the release of Ca+2ions from endoplasmic reticulum of the taste cell. The increased concentration of calcium ions in the cell leads to depolarization and release of neurotransmitters. This message is sent to the brain through sensory neuron and interpreted as "bitter" taste. [6]

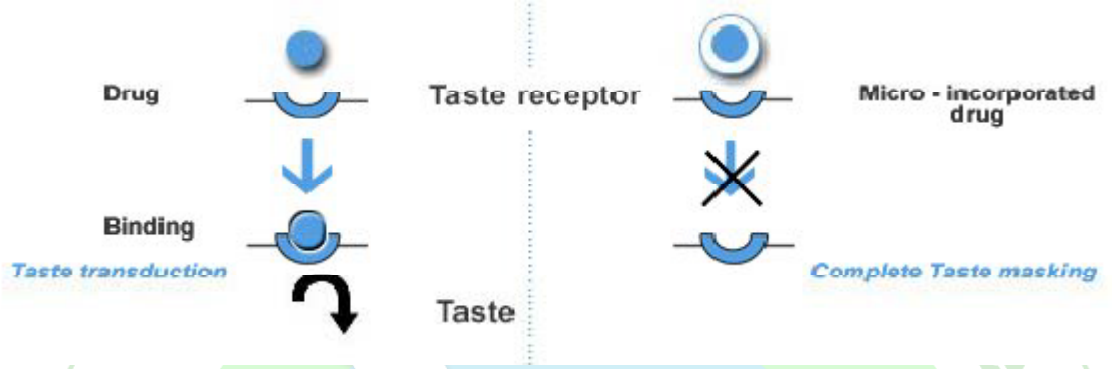


Fig. 3 Taste signaling Pathways

Effect of age on taste buds

Cells that make up the taste buds with age wear out , as a result tastebuds begin to disappear from roof and the sides of the mouth except taste buds that's are located over tongue. Remaining taste buds becomes less sensitive. Researchers have been proved that smocking and eating of scalding food may damage to taste buds. This lacking of taste may lead to loss of appetite and poor nutrition. Taste is a type of medium to experience the world of tastes for infants and young children. It is seen that children are more sensitive to certain taste than any adults. But because taste can be subjective. The mechanism that causes taste sensitivity in young sterscan be difficult to analyze. [6]

Causes of infected taste buds

Taste buds infection usually occurs due to vitamin B complex deficiency, long-term antibiotics drug therapy following radiation ,smoking, vigorous rubbing by a rough tooth and thickening of tissues in elderly and fungal infection (oral thrush) in those with decreased immunity [6]

Ideal properties for taste masking process and formulation

- An ideal taste masking process and formulation should have the following properties:
- Involve least number of equipment 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.

Factors that are taken into consideration during the taste-masking formulation

- Extent of the bitter taste of the API
- Requires 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
- Requires dosage form

TASTE MASKING TECHNIQUES [4]

- Various techniques reported in the literature are as
- Addition of flavors and sweeteners
- Coating
- Microencapsulation
- Ion exchange resin
- Inclusion complexes
- Granulation
- Adsorption
- Prodrug approach
- Bitterness inhibitors
- Multiple emulsion
- Liposome formation
- Spray dried technique
- Solid dispersion technique
- Addition of flavours and sweeteners

Flavours and sweeteners are commonly used in taste masking of bitter drugs to improve the taste of the bitter drugs.

Table 1: Examples of Flavors and sweeteners

Author	Drug	Flavour
Gohel M,11	Nimesulide	Camphor
Dandagi12	Ofloxacin	Aspartame

Coating

Coating is one of the common and efficient method used in taste masking technologies. This process involves the coating of bitter tasting drugs using various inert excipients which would help to prevent the interaction of the drug particle with the taste buds for a considerable period of time. The coating material is classified into lipids, polymers and sugars. These materials can either be used alone or in combinations, as a single layer or multiple layer coat to achieve taste masking of the bitter drugs. Hydrophobic polymers have been popularly used for coating of bitter drugs than hydrophilic polymers to achieve taste masking. These excipients are either insoluble or take sufficient time to solubilize in the presence of salivary fluid which helps to provide a physical barrier to the entrapped drug particles.

Table 2: Examples of coating

Author	Drug	Polymer
Hiroya Sugao,13	Indeloxazine hydrochloride	mixture comprising hydrogenated oil and surfactants
Shirai14	Sparfloxacin	Low substituted hydroxypropyl cellulose, ethyl cellulose

Ion exchange resin

In taste masking by ion exchange resins, the resin drug complexes formed will elute only a limited percent of drug in the saliva pH. Thus the taste of the drug is masked without interrupting the drug release profile. Taste masking by drug resin complexation is achieved when an insoluble drug reacts with suitable ion exchange resins, to form a drug resinate complex. The complex, because of its insoluble nature in the salivary conditions, exhibits no virtual taste due to which even extremely bitter tasting drugs loses their taste when converted into drug resinate. The selection of ion exchange resin for drug complexation is critical as the drug resinate should be sufficiently stable to prevent break down in salivary fluid and at the same time releases the drug completely under the gastrointestinal environmental. The drug thus released from the resinate gets absorbed in the usual way while the resin passes through the gastrointestinal tract without being absorbed.

Table 3: Examples of Ion Exchange Resin

Author	Drug	Ion exchange resin
Madgulkar, A. R.. 15	Tramadol HCl	Tulsion335
Rao C. G.G.,16	Quinine sulphate	Indion 234
Bhise 17	Diphenhydramine Hydrochloride	Indion 234
Cotteril18	Levamisole	Amberlite IRP-69
Bhelekar19	Ranitidine HCl	Indion 234
Pisal S.20	Ciprofloxacin	Indion234

Microencapsulation

Microencapsulation is a process in which the active moiety (solid or liquid droplets) is coated with apolymeric material or film.

Table 4: Examples of Microencapsulation

Author	Drug	Polymer
Al-omran21	Diclofenac sodium	Ethyl cellulose, Diethyl phthalate and polyethylene glycol

Granulation

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.

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 its oral solubility or decreasing the availability of drug to taste buds. 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 complexes. B-cyclodextrin is the most widely used complexing agent for inclusion type complexes. It is a sweet, nontoxic, cyclic oligosaccharide obtained from starch.[7]

Table 5: Examples of Inclusion complexes

Author	Drug	Polymer
Sanghavi N. M .22	Terfenadine	B-cyclodextrin

Adsorption

This process involves the adsorption of the drug solution using insoluble materials like silica gel, bentonite,veegum etc. The adsorbate (resultant powder) is dried and used for the formulation of final dosage forms. Adsorbates are commonly used with other taste masking technologies. The drug may be adsorbed or entrapped in the matrix of the porous component, which may result in a delayed release of the bitter active during the transit through the oral cavity thereby achieving taste masking

Prodrug approach

Prodrugs 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 receptor 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.

Table 6: Examples of Prodrug approach

Drug	Prodrug with improved taste
Triamcinolone	Diacetate ester
Clindamycin	Palmitate ester
Chloramphenicols	Palmitate ester

Multiple emulsion technique

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.

Table 7: Examples of Multiple emulsion technique

Author	Drug	Polymer
T. Uchida 23	Polylactic acid	NaCl , CaCl2, Brilliant blue dye

Bitterness inhibitors

The development of a specific universal inhibitor for bitter taste has been widely required in the fields of taste physiology and pharmaceutical sciences, but no such inhibitors has been available.[2]

Spray drying technique

In the present investigation, bitter taste of drug is masked by preparing microparticles of drug with certain hydrophilic polymers such as Hydroxypropyl methylcellulose (HPMC) and polyvinyl pyrrolidone (PVP) by using spray drying t echnique. The purpose of this technique is to develop the taste-masked microspheres of intensely bitter drug by spray-drying technique. By use of different polymers microspheres are formed and it is found that taste masking capacity and drug release profile was excellent. The microspheres were characterized by Fourier transform infrared spectroscopy, scanning electron microscopy, Drug loading, in vitro bitter taste evaluation, and drug-release properties. [2]

Table 8: Examples of Spray drying technique

Author	Drug	Polymer
Gedam S.S24	Diphenhydramine	hydroxypropyl methyl cellulose, Poly vinyl pyrrolidone
Shreenivas S.A., 26	Ondensetron hydrochloride	Chitosan, Methocel E15 LV, and Eudragit E100
Shirai27	Sparfloxacin	Low substituted hydroxypropyl cellulose, ethyl cellulose

Solid dispersion technique

Solid dispersion defined as dispersion of m ore active ingredients in an inert carrier or matrix at solid state prepared by fusion solvent method. Solid dispersion can also be prepared by co-precipitate method for that preparation obtained by solvent method such as coprecipitate of sulphasalazine and povidone.In this insoluble matrices or blend matrices may be used to mask the taste of drugs.[2]

Table 9: Examples of Solid dispersion technique

Author	Drug	Polymer
Shah T.J.28	Rofecoxib (RXB)	Poloxamer 188
Punit Shah .29	Artemether	Mono Amino Glycyrrh-yzinate Pentahydrate (GLY)

Liposome formation

This is another way of masking the unpleasant taste of bitter therapeutic drugs by incorporating them into liposomal formulation prepared from egg phosphatidyl choline masked the bitter taste of chloroquine phosphate in HEPES(N-2hydroxyethylerzine-n-ethane sulfonic acid) buffer at pH 7.2 [2]

Table 10: Examples of Liposome formation

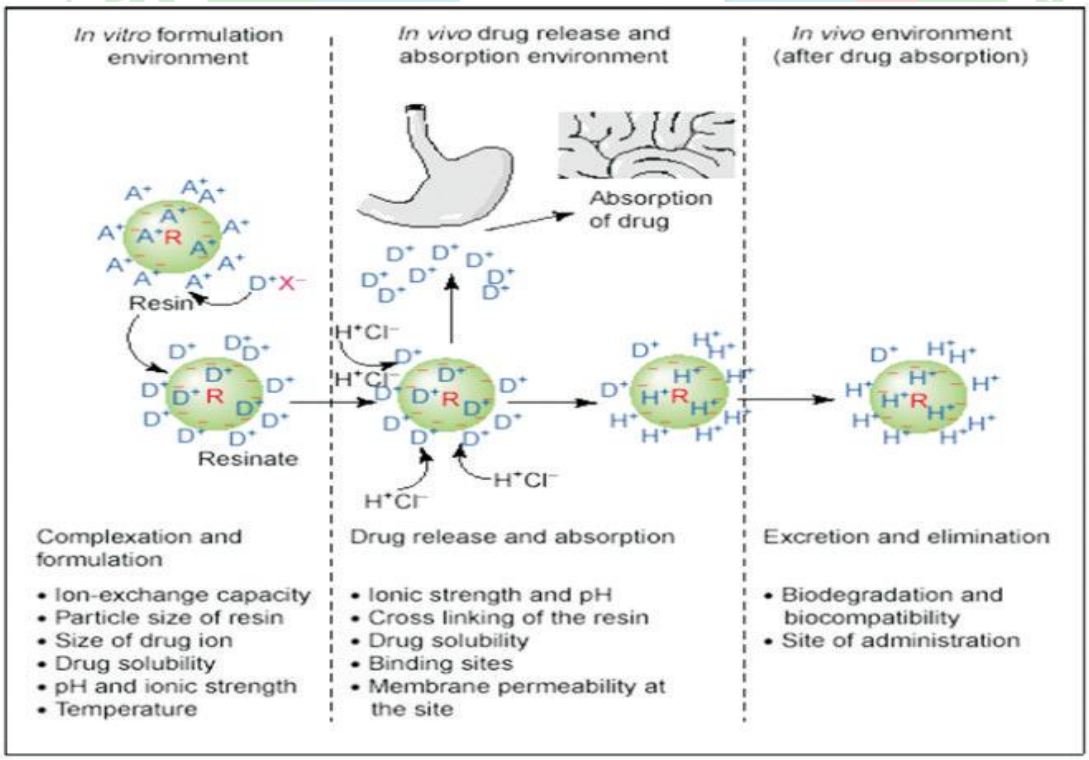
Author	Drug	Polymer
Wien T.30	Quinine, denatortium and propranolol	lipoprotein composed of phosphatidic acid (PA) and β-lactoglobulin (LG)

ION EXCHANGE RESIN

The problem of providing pediatric and geriatric patient with drug dosage forms that are palatable has been around for long time. Children and infants are most sensitive to bitter and sweet tastes than adults. Because of unpleasant taste children are frequently fail to take medications properly. Non-compliance can lead to worsening of diseased condition.

Different taste masking technologies have been used to address the problem of patient compliance. Conventional taste masking techniques such as the 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. Similarly, microencapsulation of potent bitter active agents such as azithromycin is insufficient to provide taste masking of liquid preparations.

Ion exchange resin (IER) provides alternative method for taste masking. In which 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 is such that the average pH of 6.7 and cation 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 and at the same time, its bioavailability is not affected.



Mechanism

Ion-exchange resins (IERs) are high molecular weight polymers with cationic and anionic functional groups (most common polymeric network is a copolymer of styreneand divinylbezene). Drug can be bound to the resin by either repeated exposure of the resin to the drug in achromate 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.

Properties

- Ion exchange resins are solid and suitably in soluble high molecular weight polyelectrolyte's that can exchange their mobile ions of equal charge with the surrounding medium.
- Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are there for inert.
- They have versatile properties as drug delivery vehicles, equally suitable for drug delivery technologies, including controlled release, transdermal, nasal, topical, and taste masking.

TYPES OF ION EXCHANGE RESINS [22]

Cation exchangers (Anionic resin)

Cation exchange resin is prepared by the copolymerization of styrene and divinyl benzene and have sulphonic–**232-** acid groups (-SO3H) introduced into most of benzenerings. The functional group of these resins under goes reaction (exchange) with the cations in the surrounding medium.

Mechanism:

Resin- - ax+ + C+ →Resin- - C+ +ax+

Where, Resin- indicates polymer with SO3 – sites available for bonding with exchangeable cation (ax+) and C+ indicates cation in the surrounding solution getting exchanged.

Anion exchangers (Cationic resin)

These are the polyelectrolytes under going reaction with the anions of the surrounding solutions.

They are prepared by first chlormeythylating the benzenerings of styrene-divinyl benzene copolymer to attachCH2Cl groups and then causing these to react with tertiary amine such as triethylamine.

Mechanism:Resin+ - bx - + A- → Resin+ - A- + bx-

Where, Resin+ indicates polymer with N+ sites available for bonding with exchangeable anion (bx-) and Aindicates anion in the surrounding solution getting exchanged.

METHOD

It is frequently necessary to convert a resin completely from one ionic form to another. Charged drugs are normally loaded on to

ion exchange resins by two methods, viz, column method and batch method.

Column method

In this method a highly concentrated drug solution is passed through a column of resin particles. Since there action is an equilibrium phenomenon, maximum potency and efficiency is best obtained by the column method.

Batch method

In this method the drug solution is agitated with a quantity of resin particles until equilibrium is established.

Reaction

Upon ingestion, drugs are most likely eluted from cation exchange resins by H+, Na+ or K+ ions and from anion exchange resins by Cl-, as these ions are most plentiful available in gastrointestinal secretions.

Typical reactions involved in the gastrointestinal fluids may be envisaged as follows:

In the stomach:

Re-COO-Drug+ + HCl→ Re-COOH + Drug Hydrochloride

Re-N(CH3) + 3Drug-+ HCl→ Re-N(CH3) 3Cl +Acidic drug

Re-N(CH3)+3 Drug -+ NaCl→ Re-N(CH3) 3 Cl +Sodium salt of drug

In the intestine:

Re-COO-Drug + + NaCl→ Re-COONa + Drug Hydrochloride

Re-N(CH3)+3Drug -+ NaCl→ Re-N(CH3) 3Cl + Sodium salt of drug[2]

Drug explored for taste masking

Drugs with unpleasant taste

Class	Drugs
Antibiotic	Ampicillin, Cloxacilin, Chloramphenicol, Erythromycin, Tetracycline, Ciprofloxacin
Antitussives	Codeine phosphate or sulphate, Dextromethromethorphan
Decongestants	Phenylephrinbititrate or hydrochloride, Phenyl propenolamineHCl
Laxative	Dioctyl sodium, Sulphosuccinate
Expectorant	Potasium iodide, Ethylmorphine
Antihistamines	Chlorpheniramine maleate, TripelenamineHCl
NSAIDS	Ibuprofen, Naproxen, Mefenamic acid, Fenoprofen
Antiulcer	Ranitidine, Famotidine

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