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MASKING OF BITTER DRUG BY USING ION EXCHANGE RESIN METHOD

Dighe Ajinkya D.*, Bidkar Shital J., Naykodi Pradnya S., More Komal V., G. Y. Dama

Sharachandra Pawar Collge of Pharamacy, Otur.

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***Corresponding Author**
Dighe Ajinkya D.
Sharachandra Pawar Collge of Pharamacy, Otur.

ABSTRACT

The lamivudine is bitter in taste API. Undesirable taste is one of the several important formulation problem that are encounter with certain drug the present study deals with development of taste masked resonates of Lamivudine using ion exchange resin. The drug resin complexation procedure was optimize with respect to drug to resin ratio, stirring time and pH of medium. The taste masked complex was characterized by FTIR, DSC. In-vitro release studies elevated complete drug release within 120 min in 0.1N HCL solution. The taste masked complex was than formulated into a oral film dosage form using Glycerin, pectin and citric acid. The oral film was evaluated for various quality control parameter

KEYWORDS: Bitter taste, Taste masking, oral film, lamivudine, resinate, Ion exchange resin.

INTRODUCTION[1-13,15-18]

Oral administration of the drug considered to the most acceptable route for drug delivery. The taste of any oral formulation administered, mainly the bitter drug, to a pediatric and geriatric patient has a very important effect to the adherence to drug therapy. The taste masking is a key challenge in any drug delivery system, hence drugs dissociate in the patient mouth is close closeness to taste buds, there for increasing patient compliance. A different method are presence for taste masking purpose such as microencapsulation, various polymer, coating with polymer lipid, flavor and sweetener addition also use some lipophilic vehicle to mask the bitter taste of drug or for obstructing the taste buds. These method are used to prevent instant drug release, when contact with the taste masking method, the other complexation techniques are using like ion exchange resin (IERs) is simple, cost effective and dose not

required more ingredient or organics solvent. Interpenetrating polymer network (IPN) beads have been using by many scientist for sustain release drug carrier as they have many good properties. These method was stable, biocompatible, nontoxic and biodegradable which have attracted their use in pharmaceutical industry.

IERs have excellent properties like high ion exchange ability, good administration capacity, physiochemical stability and their insolubility in any solvent make them suitable candidates as taste masking and sustain release of drug. In that taste masking drug and resin complex is achieved when an ionizable drug react with a suitable ion exchange resin to form a drug-resinate complex. Ion exchange resins (IERs) are high molecular weight polymers with cationic and anionic functional group. Ion exchange resin is water soluble cross linked polymer having salt forming groups in repeating site on the polymer chain. Drug is attached to the oppositely charged resin substrate, forming insoluble adsorbates or resinates through weak ionic bonding so that the separation of the drug-resin complex does not occur under the salivary pH state. When drug resin complex (DRC) are comes into contact with the gastrointestinal fluid, such as the acid of stomach, the DRC bound drug is released by exchange with counter ions and absorbed, while the resin passes through the GI tract without being absorbed.

Anatomy of the taste buds

Human are detects taste with taste receptor cell which are mainly onion formed known as taste buds. Human has contain almost 10000 taste buds which appear inside the foetus at about 3 month earlier than the child birth. A single taste bud must be containing 50-100 taste cells.

Taste buds are transmembrane protein which bind to the molecule and also ions to provide to rise the 5 exclusive number of taste sensations like sour, sweet, bitter, salty, as well as umami (Table 1).

In the highest point of taste buds microvillus process Stick out through the small opening that is taste pore into the oral milieu. The taste papillae can be seen on over the tongue as little red dots. Are particularly at the front of tongue these dots or taste papillae is called as “Fungiform papillae”.

The taste buds are found on 3 type of papillae on the tongue

1. Circumvallated papillae
2. Fungiform papillae
3. Foliate papillae.

Taste buds are located on the taste papillae. The microvilli of the taste cells are hold taste receptor or taste hair. The taste receptor is stimulated by food and also chemical dissolve in saliva together. The taste receptor stimulated and send nerve impulse to the brain and then identified the taste.

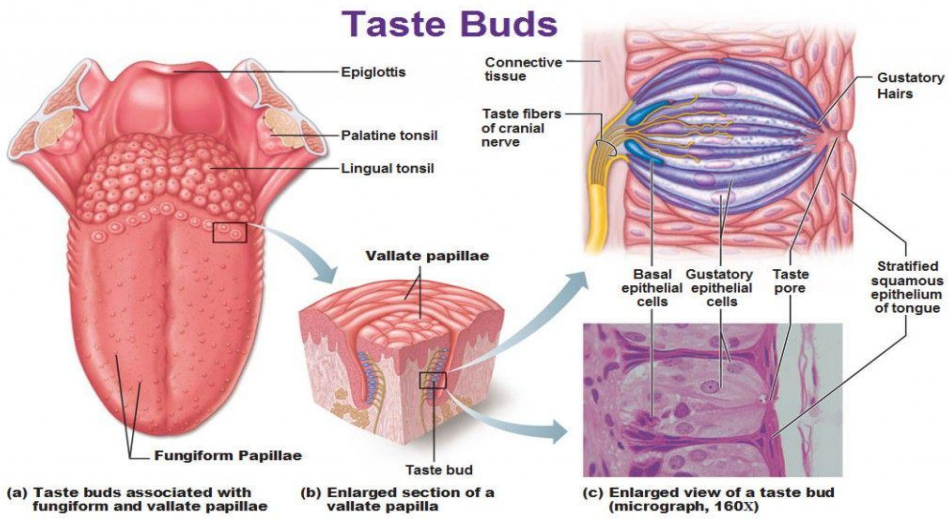


Fig. 1: Diagrammatic representation of taste buds.

Physiology of taste[2,6,10]

The human being is have around 10,000 taste buds was appear in embryo at around 90 days. In that one single taste bud contain 50-100 taste cell. Drug are interact taste buds on present in tongue to give the bitter, sweet, salty, umami taste to cause a sensation when drug was dissolve in saliva. This sensation cause a signal transudation from the taste buds. And these taste buds is produce and transfer electronic impulse in that seventh, ninth and tenth cranial nerve to the areas of the brain.

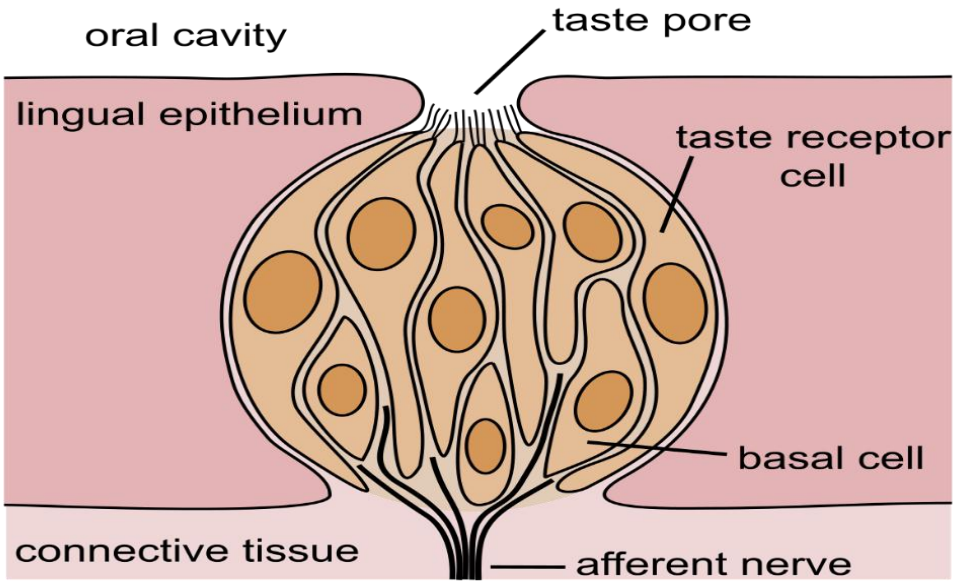


Fig. 2: Diagrammatic representation of taste.[13]

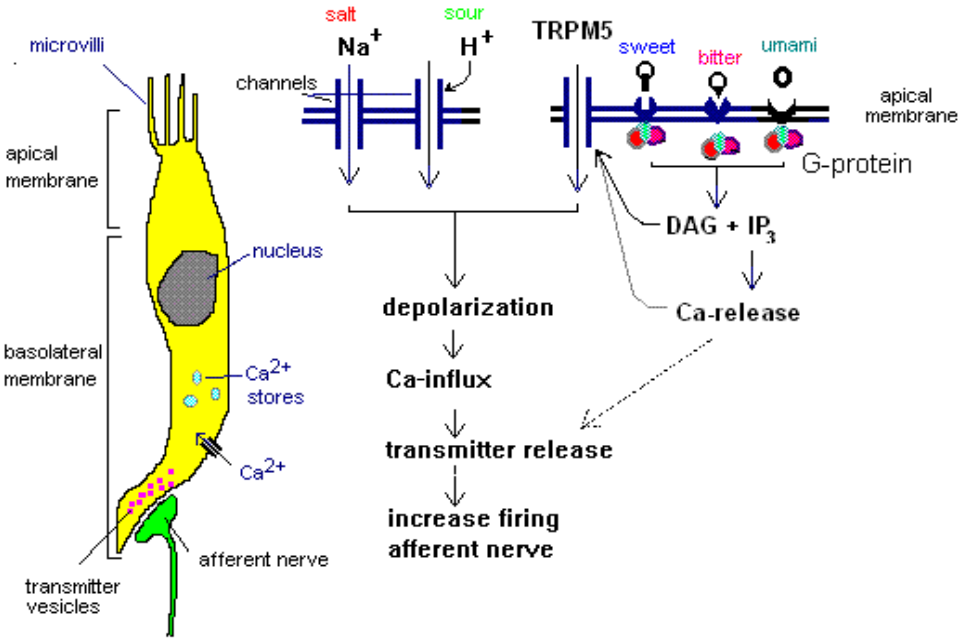
Table No 1: Physiologically human being can be detected 5 type of taste.[4,13,14]

Primary taste	Located area on tongue	Functional group	Natural source	Pharmaceutical example	Threshold conc
Bitter	Back of tongue	Organic amines	Poison, Alkaloids	Quinine, Lopiramide etc.	0.5%
Sour	Side of the tongue	Organic and inorganic acids	Natural food and spoiled food	Ascorbic acid, Malic acid	0.25%
Sweet	Tip of tongue	Sugar and sugar analogs	Nutritional and synthetic sweetener's	Fructose and saccharine	0.007%
Salty	Either side of the Upper front portion	Inorganic salt	Sea water mineral deposits	Sodium chloride	0.00005%
Umami	Middle portion of the tongue	Amino acids	Primarily from vegetable Mushroom.	Insulin and ephedrine	-----

1.3. Taste signaling pathway[6,15]

Taste transduction begins with the interaction of tastant to taste receptor cells in the taste buds. The tastant bind with G-Protein coupled receptor in the cells was triggering the release the G-Protein called as Gustducin. The sensation of taste process begins when gustducin was activates the effector enzymes such as phosphodiesterase IA (PDE) or phospholipase C beta 2

(PDC). Then the effector enzyme was change the intracellular level of second messenger in that mainly cyclic adenosine monophosphate (cAMP), Inositol, 1,4,5- Triphosphate (IP3) and diacylglycerol (DAG). The second messengers was activated ion channel including calcium channel inside the cell in that potassium, sodium and calcium channel on extracellular membrane. The ionization process cause the cell depolarization and release the neurotransmitter that send nerve impulse to the brain that carries the signal of bitter taste and taste blockers work by interfering with taste transduction.



.Fig. 3: Taste signaling pathway.[15]

1.4. Chemistry of ion exchange[5]

In ion exchange resin is a polymer that contain solid with charge sites that ions exchange and certain mineral called as Zeolites are a quite good exchangers. Which there are numerous functional group that have charge only are commonly use for man-made ion exchange resin.

Following basic concept was followed with ion exchange resin process

1. – COOH, which are weakly ionized by $–COO^-$.
2. – SO_3H, Which are strongly ionized by – SO_3^-.
3. – NH_2, Which weakly interact with proton to form by NH_3^-.
4. Secondary and tertiary amine that also interact proton weakly.

1.5. Taste masking[10,14]

Taste masking is define as any suitable agent was used an reduce unpleasant taste of bitter drug. Various taste masking method was involves various physical and chemical method was use to prevent bitter or unpleasant taste of drug.

Mainly two approaches are commonly used to minimize the unacceptable taste of API

1. By reduce the solubility of drug in the pH of saliva.
2. By alter the affinity and nature of drug which will be interact with taste receptor

1.6. Ideal taste masking process and formulation by following properties[6,14]

1. Involvement of minimum number of equipment and processing steps no to be a largest.
2. Should not effect on bioavailability of the drug.
3. The used excipient should be economical and easily available.
4. Minimum manufacturing cost.
5. The process and used excipient should be carried out in room temperature.
6. Excipient which have use in largest margin of safety.
7. Formulation it should be easy and rapid to prepare.
8. Minimum quantity of excipient and ingredient for most excellent component.

1.7. What factors are taken into consider during the taste masking formulation process

1. Extent of the bitter and sour taste of drug.
2. Dose loading.
3. Drug which have particular shape and size distribution
4. Drug ionic and solubility characteristic.
5. Distribution from and length of drug particulate.
6. Correct bioavailability.
7. Correct release profile.
8. Accurate dosage form.

1.8. Method of taste masking technologies[2,9,10,13,14,15,16]

i. Taste masking with flavors, sweeteners, and amino acid.

ii. Polymer coating of drug.

iii. Inclusion complexes.

iv. Ion exchange complexation.

v. Solid dispersion.

vi. Microencapsulation.
vii. Prodrug approach
viii. Development of liposome
ix. Multiple emulsion
x. Taste masking absorption.
xi. Taste masking with Lipophilic vehicle like lipid and lecithin
xii. Taste flavour enhancer and potentiators
xiii. Taste masking by gelatin
xiv. Salt formulation and derivatives
xv. Use amino acid and protein hydrolysates
xvi. Miscellaneous.

a. By effervescent agent
b. pH modifier
c. Continuous multipurpose melt technology (CMT)
d. Wet Spherical Agglomeration:

i. **Additional of flavoring, sweetening agent and amino acid**[6,10,17]

It's a common method to use taste masking of bitter API formulation. But it use is limited to highly bitter actives drug.

- **Sweeteners**[2]

Sweeteners are commonly used in combination of other taste masking methods. They can mixed with bitter taste medicament to improve the taste.

- **Classification of sweeteners**

i. **Natural sweeteners:** Sucrose, Glucose, Fructose, Sorbitol, Mannitol, Honey, Glycerol, liqurice
ii. **Artificial sweeteners:** Saccharin, Saccharin sodium, Aspartame**.**
iii. **Nutritive sweeteners:** Sucrose, Fructose, Glucose
iv. **Non-Nutritive sweeteners:** Aspartame, Sucralose, Neotame
v. **Polyols:** Mannitol, Sorbitol, Xylitol, Erythritol
vi. **Novel Sweeteners:** Trehalose, Tagatose.

Following table gives a compilation of most common artificial and natural sweeteners with their relative sweetness to sucrose and comments pertaining to each.

Table No 2: Relative sweetness of commonly used sweeteners.[17]

Sweetening agent	Relative sweetness	Comment
Aspartame	200	Not very stable in solution
Acesulfame potassium	137-200	Bitter after taste if used in higher concentration
Cyclamate	40	Banned
Glycyrrhizin	50	Moderately expensive
Lactose	0.16	Large amount required
Mannitol	0.60	Negative heat of solution
Saccharin	450	Unpleasant after taste
Sucrose	1	Most commonly used
Sucralose	600	Synergistic sweetening effect

- **Flavors[6,16]**

Pharmaceutical flavors are classified as natural, artificial, or natural and artificial which are obtained by mixing the natural and synthetic flavors. Which can used in different concentration such as Anise (3000ppm), Cardamom (550ppm), Wild cherry (50-800PPM), Lemon (1-35 ppm), Orange(500ppm), Peppermint(5000ppm). natural flavors are generally less active that the combination of natural and artificial flavors.

- **Classification of flavors[6,16]**

i. **Natural flavors:** Raspberry juice, liquorice extract, Lemon and orange spirits, Blackcurrant syrup, Ginger tincture, Anise and cinnamon aromatic waters, Peppermint and lemon aromatic oil

ii. **Synthetic flavors:** Alcoholic solution, aqueous solution, Powder.

Table no 3: Flavors selection.[19]

Taste	Recommended masking agent
Salt	Butterscotch, Apple, Apricot, Peach, Vanilla
Bitter	Wild Cherry, Walnut, Chocolate, Mint Combination, Passion Fruit
Sweet	Fruit and Berry, Vanilla
Sour	Citrus Flavor, Licorice, Rasp berry
Metallic	Berries, Mints, Grapes, Marshmallow, Gurana

- **Amino acid**

Amino acid their salt (Alanine, Taurine, Glutamic acid, Glycine) in combination with bitter drug reduce the bitterness of the drug for example, taste of ampicillin improved markedly by preparing its granules with glycine and mixing them with additional quantity of glycine, sweeteners, flavors and finally compressing them into tablets.

ii. Polymer coating of drug[6,49]

Polymer coating is one of the most important factor to be considered in the taste masking microencapsulation is selection of coating polymer. The coating is act as a physical barrier to the drug particle, there by minimizing interaction between the drug and taste buds. Polymer are mainly insoluble at saliva ph6.8 but readily dissolve at gastric fluid pH1. 2 could be good candidate for taste masking.

Table no 4: Taste masking by polymer coating.

Drug	Technique	Polymer used
Pseudoephedrine (Antihistaminic)	Emulsion solvent evaporation	Eudragit E
D-Indibufin(inhibitor of platelet aggregation)	Fludized bed dryer	Eudragit E-100, RS/RLEthyl Cellulose
Clarithromycin(Antibiotic)	Phase separation coacervation	Eudragit E-100
Ranitidine(Antiulcer)	Emulsion nonsolvent evaporation	PEG, Ethyl Cellulose
Oxybutinin(Antihistaminic)	Dispersion coating	Eudragit E-100
Belamide(Antiepileptic)	Phase separation coacervation	Gelatin
Indeloxazine(Cerebral activator)	Fludized bed dryer	Hydrogenated oil and surfactants
Cefuroxime axetil(antibiotic)	Emulsion solvent evaporation	Eudragit E-100, Eudragit L-100, Eudragit RL-100

iii.Inclusion complex[15,45,46,47]

The inclusion complexion, host molecules has a cavity in which the gust drug occupies and the taste of the gust drug masked by mainly two approaches are involve in that process.

- By minimize oral solubility in ingestion
- By minimizing the amount of drug particle exposed to taste buds, decreasing the perception of better drug

Cyclodextrins are commonly used in industry due to their ability to form inclusion complex. CD is a sweet, nontoxic, cyclic oligosaccharide obtained from starch. The inhibition of bitter taste by cyclodextrins was in increasing order of alpha, gamma, beta cyclodextrin.

Table no 5: Various complexing agent used for taste masking of bitter drug.[16]

Durg	Category	Complexing agent
Zinc acetate dehydrate	Recovery of zinc deficiency	Anethol-β-cyclodextrin complex and saccharin
Carbapentane citrate	Local anesthetic	Cyclodextrins
Ibuprofen	NSAID	Hydroxypropyl β-cyclodextrin
Gymnema sylvestre	Anti-diabetics	β–Cyclodextrin, Chitosan
Dioscin	CVS disorder	β–Cyclodextrin
Benexate hydrochloride	Antiulcer	β–Cyclodextrin
Metronidazole benzoate	Antibacterial	γ-Cyclodextrin
Hexitidine	Antibacterial	β–Cyclodextrin
Zipeprol	Antitussive	β–Cyclodextrin
Guaiacol	Anti diarrhetic	β–Cyclodextrin
Levosulpride	Antipsychotic	β–Cyclodextrin
Chloroquine phosphate	Antimalarial	Tannic acid
Dimenhydrinate	Antiemetics	Eudragit-S-100

a. Ion exchange complexation[8,20]

The taste masking by Drug: resin complexation is achieved when an ionizable drug react with a suitable ion exchange resin to from drug resinate complex (Nanda and Garg 2002). IERs are the high molecular polymer with anionic and cationic functional group. IER have a excellent properties like high ion exchange capacity, for good absorption capacity, physic-chemical stability and their insolubility in any solvent make them suitable candidate as taste masking and sustain release of drug.

IER are high molecular weight insoluble polymer containing loosely held ions which have the ability to exchange other is in solution which come in contact with them. The ion exchange resin are generally classified on cationic exchanger and ionic exchanger, which is based on the type of ions to be exchanged. Cationic exchanger have positively charged mobile ions and anion exchangers negatively charged exchangeable ion. Hence ionizable group attached to the hydrocarbon network of resin structure determined the chemical behavior of resin. The resin are mainly classified as strong and weak acid cation exchangers or strong or weak base anion exchangers.

A. Classification[8]

1. Cation exchange resin

- ✓ Strong Acid: e.g. Sulphuric acid
- ✓ Weak Acid: e.g. Carboxylic acid

2. Anion exchange resin

- ✓ Strong base: E.g. Quaternary amine
- ✓ Weak base: E.g. Predominantly tertiary amine substitute

1. Cation exchange resin

$$\text{Resin-COO-H}^{+} + \text{Basic Drug}^{+} \longrightarrow \text{Resin-COO-Drug}^{+} + \text{H}^{+}$$

✓ **Strong acid cation exchange resin**

The principal sulfonated styrene-divinylbenzene copolymers are employed as strong acid cation exchange resins. These are spherical resin prepared by the sulphonation of styrene-divinylbenzene copolymer bends with sulfonating agent of choice E.g. Suphuric acid, Chlorosulfomic acid and Sulfur trioxide.

✓ **Weak acid cation exchange resin**

The cross linking an unsaturated carboxylic acid like methacrylic acid with a cross linking agent such as divinyl benzene results in these preparation of these resins. These resin function pH 6. These type of ion exchange resins are used for taste masking of bitter drug containing –COOH functional group. Weak cation exchange resin are the most commonly used resin in taste masking of pharmaceutical purpose.

2. Anion exchange resin

$$\text{Resin-N(CH}_3\text{)} + 3\text{Cl}^{-} + \text{Acidic drug} \longrightarrow \text{Resin-N(CH}_3\text{)} + 3\ \text{drug}^{-} + \text{Cl}^{-}$$

✓ **Strong base anion exchange resin**

The quaternized amine resins prepared by the reaction of triethylamine with chloromethylated copolymer of styrene and divinylbenzene. Apart from pharmaceutical taste masking, these types of resins also found application in deionization of water and in pharmaceutical analysis as a separation media for thin layer chromatography.

✓ **Weak base anion exchange resin:**

The primary and secondary amines or ammonia react with chloromethylated copolymer of styrene and divinylbenzene to form these resin. These weak base anion exchange resin function well below pH 7. These resin found application in chemical industry and in pharmaceutical analysis

B. Preparation of resinate[8]

The mainly two method are employed to preparation of resinate. Batch method and column method was used to prepare Drug: Resin complex.

a. Batch method

In this method, an ion exchange resin is added to water in order to make its slurry. The accurately weighted quantity of drug is then added to this slurry which followed by stirring to prepare the complex. After the formulation of complex, it is washed with water and dried. Mixing time of drug and resin, pH, Temperature and swelling of resin and Drug: Resin ratio is several factors, which can affect the complexation of drug with resin.

b. Column method

The typical column procedure the resin is slurry in water and added to a column and backwashed with water to remove air pockets and distribute the drops. 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 absorbed a carboxylated drug on ion exchange resin, using NaOH to convert the resin to basic cycle.

The Batch method is always chosen over than the column method is case of preparation taste masked ion exchange resinates. The major motive behind that the fine particle of the ion exchange resins which does not allow them to be used in columnar operations due to chances of washing away during operating. Higher swelling efficiency in the batch process makes more surface area available for ion exchange.

C. Factor affecting ion exchange resin complex[7,8]

a. Particle Size and form

The size of resin particle affect the rate of ion exchange process. The minimum size of a resin particles result is reduce time required reaction to reach the equilibrium with the surrounding medium.

b. Cross linking

The percentage of cross linking affect the physical structure of resin particles. The resins with low degree of cross linking can take up large amount of water and swell into a structure that is gelation and soft. Cross- linking also affect the loading efficiency of resin by affecting its porosity and swelling properties.

c. Exchange capacity

The exchange capacity refers to the number of ionic sites per unit weight or volume (meq per gram or meq per ml). The exchange capacity determines the amount of drug that can be absorbed on a resin hence the potency of complex.

d. Effect of temperature

The certain resin the effect of temperature on drug loading has been reported. High temperature any also cause swelling of resin. Cation exchange resin does not get expressively affect by temperature changes anion exchangers.

e. Mixing time

The increase in mixing time enhance the swelling of resin which ultimately result in improve drug loading. Minimum mixing time result in improper swelling and reduced percentage of drug complexation.

f. pKa

The pka value of the resin is taking important effect on the rate at which the drug is free from the resinate in the gastric fluid. pKa of drug also decide the extent of dissociation and complexation with the resin. If the pH is higher than pKa of drug, the drug remain mostly is nonionized from resulting in reduce complexation. At a certain pH, wherein, both the drug and the resin are ionized in adequate quantity, resulted in maximum resinate formation.

g. Porosity and swelling

Porosity affects the capacity of ions to enter into a resin matrix and thus the efficiency of complexation. The quantity of cross linking substances used in polymerization method determines the porosity of resin. The amount of swelling is directly proportional to the number of hydrophilic functional groups attached to the polymer matrix and inversely proportional to the degree of DVB cross linking present in the resin.

Table no 6: Commonly used IER for taste masking.[7]

Resin			**Medicament**
Name	**Functional group**	**Polymer backbone**	
Amberlite™ IRP64	Weak acid COO^-	Cross linked polyacrylic	Dextromethorphan, Dimenhydrinate
Amberlite™ IRP96	Strong acid SO^{3-}	Styrene- Divinyl benezene	Ranitidine
Amberlite™ IRP88	Weak acid COO^-	Cross linked polyacrylic	Talampacillin-HCL, Paroxetine
Indion 204	Weak acid COO^-	Cross linked polyacrylic	Norfloxacin, Ofloxacin

Indion 214	Strong acid COO^-	Cross linked polyacrylic	Azithromycin
Indion 234	Weak acid COO^-	Cross linked polyacrylic	Ciprofloxacin, Chloroquin Phosphate
Kyron T-104	Weak acid COO^-	Cross linked polyacrylic	Cefpodoxime Proxetil
Kyron T-114	Strong acid COO^-	Cross linked polyacrylic	Ofloxacin
Kyron T-134	Weak acid COO^-	Cross linked polyacrylic	Meyronidazole

Table 7: List of commonly used ion exchange resin.[21-28]

Type of resin	Functional group	Functional backbone	Commercial resins
Strong anion	$-NR_3$	Polystyrene-DVB	Ambrelite IR 400, Dowex 1, Indion 454, Duolite AP 143
Weak anion	$-NR_3$	Polystyrene-DVB	Ambrelite IR 120, Dowex 2
Strong cation	$-SO_3H$	Polystyrene-DVB	Ambrelite IR 120, Dowex 50, Indion 244, Purolite C100, HMR, Kyron –T-154
Strong cation	$-SO_3Na$	Polystyrene-DVB	Ambrelite IRP 69, Indion 254, Tulsion-T- 344
Weak cation	-COOH	Methacrylic acid-DVB	Ambrelite IRC 50, Tulsion-T- 335, 339, Indion 204-234, Purolite C102DR, Kyron-T-104, Doshion P544(R)
Weak cation	-COOK	Methacrylic acid- DVB	Ambrelite IRP88, Indion 234, Tulsion-T-339, Kyron-T-134.

Table No 8: Application of IER Complexation in taste masking and their dosage form.[8]

Drug	Resin used	Dosage Form
Chlorpheniramine maleate	Indion CRP 244, 254	Resinates in powder form
Ranitidine HCL	Amberlite IRP 69/88	Chewable tablet
Buflomedil	Amberlite IRP 69	Resinate in powder form
Orbifloxacin	Amberlite IRP 64/69	Dry/liquid suspension
Risperidone	Amberlite IRP 64	Fast disintegration tablet
Quinine Sulphate	Amberlite IRP	Oral Suspension
Roxithromycin	Amberlite IRP 64	Mouth dissolve tablet
Dextromethorphan	Amberlite IRP 69	Fast Melting tablet
Risperidone	Amberlite IRP 64	Resinates in powder form
Ondansetron HCL	Indion 234	ODT
Etoricoxib	Indion 204	Resinates in powder form
Donzepezil	Amberlite IRP 64	ODT

Table no 9: Patent related taste masking composition including ion exchange resin.

Drug	Inventor and Year	Patent No
Ketoprofen	LI Michael H.C., Kurmme M., 2012	WO2012/167878A1
Siladenafil	Murpani D., 2012	WO2012/120522A1
Anti-retroviral	Kakumanu V. K., Isloor S.,Arora, 2011	WO2011/080683A1
Phosphodiesterase-5(PDE-5) inhibitors	Pilgaonkar P. et al. 2011	WO2011/030351A2
Escitalopram	Murpani D., Pandora A. 2011	US2011/0300224A1
Active drug	Hargens R.D. et.al	US80088378B2
Pregabilin	Huda I., et. Al. 2010	WO2010/150221A1
Sildenafil citrate	Singh S., et.al, 2009	WO2009/074995A1
Active drug	Hargens R.D. et.al, 2008	US2008/0044371A1
Levocitrizine dihydrochloride	Anterkar A.K., et.al, 2008	US2008/0095842A1
Active drug	Becicka B.T., et.al, 2007	WO2007/146293A3
Dextromethorphan	Bees W.S., et.al, 2006	US2006/0204559
Active drug	Jeong S., et.al., 2006	US2006/0115529
Active drug	Gole D., et.al., 2005	US2005/0036977
Active drug	Hergens R. D. et.al., 2005	WO2005/013934A2
Active drug	Mukhargi G, et.,al 2003	US6,565,877,B1
Dextromethorphan	Bees W.S., et.al,2001	WO01/70194A1
Ranitidine	Douglas S.J. Bird F.R. 1991	US5032393
Active Amino or amino group	Damani N.C., Tasu J.H.1998	EP0212641
Quinolones	Gao R., et al 2001	US6,514,492B1

Table no 10: Patent work of resinate for sustained release formulation.[29-43]

Drug	Polymer	Formulation	Patent no.
Cimetidine, Ciprofloxacin	Amylose Starch	Sustained drug release formulation	US8414919
Active drug	Resin	Sustained drug release formulation	WO/2012/063257
Morphine, ibuprofen, Codeine	HPMC	Modified release formulation	US8337890
Oxycodeine, Albuterol, Methylphenidate, Dextromethorphan	Ambrelite, IRP-69	Modified release formulation	US8062667
Venlafaxine HCl, Diclofenac sod.	HPMC K100M	Sustained drug release formulation	US20110136921
Pseudoephedrin, Chlorpheniramine, Hydrocodone	Ambrelite IRP-69	Extended release formulation	WO/2010/127100
Chlorpheneramine, polistirex, sod. Polysterene	Ambrelite IRP-69	Polymer coated drug-resin exchange resins method	USP20080118570

sulfonate.			
Chloroquine and pyrimethamine	HPMC K100M	Sustained drug release formulation	USP20070128269
Oxycodone, Meperidine, Methadone, Nalbulphire, Opium, Pentazocine.	Styrene-divinyl benzene	Opioid Sustained drug release formulation	USP20060263431
Hydrocodone, bitartrate	Dowex 50 WX8H	Sustained drug release formulation	USP20050265955
Dihydrocodeine phosphate, Codeine phosphate, Noscapine HCl	Ambrelite IR-120	Sustained drug release formulation	WO/2003/020242
Butorphanol, Fentanyl, Codeine, Dihydrocodeine	Hydroxyalkylcellulose/ SVB	Opioid Sustained drug release formulation	USP20020164373
Pilocarpine, Epinephrine	Poly(styrene-divinyl benzene)	Sustained release ophthalmic formulation	USP6258350
Phenyl propenolemine	SVB	Sustained release oral formulation	USP5186930
Betaxolol, Befumolol	Ambrelite, dowex	Sustained release composition and polycaroxylic polymer	EP0429732

Table 11: Examples of drug taste masked by ion exchange resins.[21,44]

Drug	Resin used
Azithromycin	Dowex, Indion 234, Indion 214, Kyron T114, Indion 204
Amphetamine	Ambrelite IPR69
Amodiaquine HCl	Kyron T-134
Ambroxol HCl	Indion 244, Indion 204, Indion 234
Buflomedil	Ambrelite IPR69, Tulsion T344, Indion 244
Beta lactum ATBT	Ambrelite IPR88, Rosin 134
Beta histidine HCl	Tulsion T344
Chloroquine phosphate	Polyacrylic acid, ambrelite IPR 88, Indion 234, Indion 294, Tulsion T 339
Ciprofloxacin	Lewatit CNP, Tulsion T339, Indion 234, Indion 294
Clarithromycin	Carbomer 934, Tulsion 335
Chlorpheneramine maleate	Indion CPR 244, Indion CPR 254, Dowex 50
Clopidogrel sulphate	Water soluble cation exchange resin with sulphonic acid group.
Cefuroxime axetil	Kyron T 104, indion 214, Indion 234, Indion 414
Cefpodoxime proxitil	Kyron T 104, duolite AP143
Codeine	Ambrelite IPR69
Cetirizine dihydrochloride	Tulsion 339, tulsion 335
Dextromethorphan HCl	Carbomer 934
Dicyclomine HCl	Ambrelite IPR120, Dowex 50, Kyron T154, Indion

	214, Indion 244
Dimenhydrinate	Ambrelite IPR50, Indion 204
Doniperil chloride	Ambrelite IPR64
Diphenhydramine HCl	Indion 234, Tulsion 343, Indion CPR244, Indion 254
Dextroamphetamine	Tulsion
Doxylamine succinate	Indion 234, Indion 204, Indion 414
Diclofenac	Ambrelite IRA900
Diclofenac sodium	Duolite AP143
Ephedrine HCl	Ambrelite IR 120, Indion CPR 244, Indion CPR254
Erythromycin	Carbomer 934, Indion 204, Kyron T114, Doshion P542
Erythromycin stearate	Ambrelite IR 120, Dowex 50, Indion 244, Kyron T154
Erdosteine	Doshion P544
Etoricoxib	Indion 204, Indion 214, Indion 234, Indion 414
Enorfloxacin	Ambrelite IPR64
Famotidine	Indion 214, Ambrelite IPR69
Fexofenadine HCl	Indion 234
Floroquinolone	Tulsion 344, Indion 204
Levamisol	Ambrelite 64, Ambrelite IPR69
Levocitrizine	Kyron T104, Indion 204, Tulsion335
Metronidazole	Ambrelite IR48, Kyron T114, Indion 234, Kyron T134
Metoclopramide	Indion 204, Indion 214, Indion 234.
Metoclopramide HCl	Indion 204
Metformin HCl	Indion 254
Mefenamic acid and paracetamol	Doshion 544P, Kyron T134
Norfloxacin	Doshion P544(R), Indion 204, Tulsion 335, Kyron T104, Ambrelite IRC50
Orbifloxacin	Ambrelite IPR64, Ambrelite IPR69, Doshion P544(R)
Ofloxacin	Tulsion T335, Kyron T114, Indion 204, Indion 214
Ondensatron HCl	Indion 234, Indion 294, Indion 204, Eudragit E100
Paroxetrine HCl	Ambrelite IPR88
Pseudoephedrine	Tulsion T344, Indion 244
Paracetamol	Tulsion 339
Propranolol HCl	Tulsion
Poracrillin K	Indion 234
Quinine	Dowex
Quinine sulphate	Ambrelite IPR
Ranitidine HCl	Ambrelite IRP88, Ambrelite IPR 69
Risperidone	Ambrelite IRP64
Remacemide HCl	Ambrelite IPR64
Roxythromycin	Ambrelite IRC 50, Purolite C102DR, Indion 214
Ranitidine	Indion 244, Tulsion T344
Rizatriptan benzoate	Indion 204, Indion 214
Rapimelt	Kyron T134
Spiramycin	Ambrelite IRP64

Sumatriptan succinate	Kyron T114
Tramadol HCl	Tulsion T335, Kyron T114
Topiramate	Kyron T114, Kyron T134, Doshion T542
Tinidazole	Kyron T114, Kyron T134, Indion 204, Indion 214, Indion 294, Indion 234, Doshion T-542
Zopiclone	Kyron T114
Zolpidem	Tulsion T335

b. Solid dispersion method[49]

Solid dispersion is defined as dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by fusion or melting solvent method. Solid dispersion of drug with the help of polymer, sugar, or other suitable agent, is very useful for taste masking purpose. Carriers used in solid dispersion system including ovidone polyethylene glycols, HPMC, urea, mannitol and ethylcellulose.

- **Verious approaches for preparation of solid dispersion are described below**

a. Melting method

In that method, the drug or drug mixture and carrier are melted each other by heating. The melted mixture is cooled and solidified rapidly in an ice bath with continue stirring. The final damp mass is crushed and pulverized.

b. Solvent method

In that method, the API and carrier are dissolved in common solvent, followed by solvent evaporation and recovery of solid dispersion.

c. Melting-Solvent method

In that method drug in solution is incorporated into molten mass of polyethylene glycol at temperature 70ºC without removing the solvent.

Table 12: Taste masking by solid dispersion technique.[50-61]

Drug/ active ingredient	Formulation type	Method	Polymer used
Artemether	Rapid disintegrating tablet	Solvent evaporation	Monoammonium glycyrrhizinate pentahydrate
Atenolol	-	Solvent evaporation, hot melt method, kneading method	β cyclodextrin, PEG6000, HPMC E4
Drotoverine	Tablet	Melting method	Urea, mannitol
Promethazine HCl	Fast disintegrating tablet	Solvent evaporation	Eudragit E 100
Ondansetron	Fast dissolving tablet	Solvent evaporation,	Eudragit E100

HCl		Fusion method	
Risperidone	Fast disintegrating tablet	Solvent evaporation method	β cyclodextrin, crosspovidone, crosscarmellose
Cefpodoxime proxetil	Dry syrup	Solvent evaporation	Eudragit EPO, Steric acid
Lamotrigine	Oral disintegrating tablet	Kneading method	PVP K-30 and β cyclodextrin
Rosuvastatine	Mouth dissolving tablet	Solvent evaporation	Eudragit EPO
Irbesartan	Fast disintegrating tablet	Solvent evaporation, kneading	Solplus, PEG-6000
Primaquine phosphate	Rapid disintegrating tablet	Solvent evaporation	Monoammonium glycyrhizzinate pentahydrate
Sumatriptan	Sublingual tablet	Melting method	Mannitol

d. Microencapsulation method[15]

Microencapsulation is a process in that active moiety is coated with a polymetric material or film. Coating the drug particle created a physical barrier between the taste buds and drug and hence active taste is masked. Microencapsulation is good technique applicable to protect material from volatilizing, oxidation as well as to masked their unaccepted taste for human The pH independent water soluble polymer have been used with enteric polymers, inorganic or organic pore formers to achieve taste masking by microencapsulation. Buffering agent are also include in suspending agent to increase masking efficiency of microcapsules in oral suspension. Main advantage for that method is due to the low particle size distribution of microcapsules that can remain suspended for long time

The microencapsulation are accomplished by following method[15]

- Air suspension coating
- Coacervation phase separation
- Spray drying and spray congealing
- Solvent evaporation
- Multiorifice centrifugal process
- Pan coating
- Interfacial polymerization

Table no 13: Taste masking of bitter drugs by microencapsulation.[15]

Drug	Method	Polymer	Result
Ibuprofen	Air suspension coating	Methacrylic acid copolymer	Chewable taste masked tablet having controlled release characteristics by fluid coating, obtain
Indeloxazine	Fluidized bed with side spray method	Hydrogenated oil and surfactant	Taste masked of drug without loss of bioavailability by heat treatment of wax coated microparticles.
Beclamide	Simple coaceration	Gelatin, anhydrous sodiumsulfate coacervating agent	Core:wall ratio 1:1 microencapsulation to mask bitter taste
Clarithromycin	Spray congealing	Amino alkyl methacrylate polymer E(AMCE)	Taste masking prevented by drug release in the mouth while ensuring rapid release in GIT
Prednisolone	Solvent evaporation technique	Eudragit E 100	Drug polymer 1:10 microspheres of drug are tasteless, further used for formulation in ODT
Chloroquine diphosphate	Coacervation phase separation	Ethyl cellulose	Taste masking achived

c. Prodrug approaches

Prodrug is chemically modified inert drug precursor which upon biotransformation liberates the pharmaceutically active parent compound. A combination of the factor is perhaps operative in the demonstrations of the taste response molecular geometry is one of them. E.g. bitterness of the molecule, may be due to the efficiency of the taste receptor substrate absorption reaction, which is related to the molecular geometry of a substrate. If any alteration of the parent molecule occurs by derivative formulation, the geometry is altered, affecting the absorption constant.

Table no. 14: Some example of prodrug to bitter taste masking.[10,13,19]

Parent molecule	Prodrug
Linomycin	Phosphate or alky ester
Clindamycin	Alkyl ester
Chloramphenicol	Palmitate or phosphite ester
Triamcinolone	Triamcinolone diacetate ester
Tetracyclin	3,4,5- trimethoxy benzoate salts
Morphine	N-Oxide derivatives of all morphine
Norfloxacin	Norfloxacin alkyl carbamates
Gabapentin	gabapentin 13512
Triamcinolone	Triamcinolone diacetate ester
Erythromycin	Erythromycin propionate

d. Development of liposome[10,13]

Liposome is simple microscopic vesicles in an aqueous volume is entirely closed by membrane composed of lipid molecules, lipid bilayers mainly made by natural or synthetic phospholipids. Bitter substances are commonly hydrophobic in nature. The bitter taste chloroquine phosphate in HEPES (N-2-hydroxyetylpiperzine-N'-2-ethane sulfonic acid) buffer was masked at pH 7.2 by incorporating into a liposomal formulation prepared with egg phosphatidyl choline. Bitter taste of polymyxin B sulfate and trimethoprim sulfamethoxazole have been masked by BMI 60 obtain by fractionating soy lecithin.

Table no. 15: Taste masking of drug by liposomes method.[15,50]

Drug	Polymer	Result
Chloroquine phosphate	Egg phosphatidyl choline	Chloroquine phosphate was taste masked at pH 7.2 by incorporating into a liposomal formulation
Quinine, Denatortium and Propranolol	Lipoprotein composed of phosphatidic acid and β – Lactoglobulin	PA-LG effectively suppressed the bitter taste of the drugs.

e. Multiple emulsion[16,48]

The w/o/w or o/w/o types multiple emulsion are vesicular systems in which active ingredient can be entrapped in internal phase. The entrapped substances can be transferred from internal phase to external phase through the membrane phase. This phase control the release of drug from system. If the system is stable enough for a reasonable shelf life, the formulation could also mask the taste of drug. Both w/o/w or o/w/o multiple emulsion or chloroquine phosphate have been prepared and reported to be partially effective in masking the bitter taste of drug.

f. Taste masking adsorption[2]

Adsorbate of the bitter drug tasting drug can be consider as a less saliva soluble version of these drug. Adsorption involves preparing a solution of the drug and mixing it with insoluble powder that are absorb the drug, remove the solvent, drying the final powder and then using this dry adsorbate in the preparation of the final dosage from.

Table no 16: Taste masking by absorption method.[2]

Drug	Adsorbate	Result
Loperamide	Magnesium aluminium silicate	Further granulating with hydrophobic polymer to achieve taste masking

g. Taste masking with Lipophilic vehicle like lipid and lecithin[49]

Oil, surfactant, polyalcohol, and lipid are effectively induce the viscosity in the mouth and coat the taste buds and therefore they are potential taste masking agent. The acetaminophen granules are sprayed with molten stearyl stearate, in mixed with suitable tablet excipients and incorporated into a taste masked, chewable tablet preparation. Preparation with a large excess of lecithin or lecithin-like substances are claimed to prevent bitter taste in pharmaceuticals. The magnesium aluminum silicate with soybean lecithin is used to mask the unpleasant taste of talampicillin HCL.

h. Flavour enhancer and potentiator[15]

Sugar, carboxylic acid (citric, malic, and tartaric acid), common salts (NaCl), amino acid, some other amino acid derivatives such as Mono sodium glutamate(MSG) are often employed. The potentiators are improve the perception of taste of sweeteners and make the unpleasant taste. Various potentiates include neohesperidine dihydro chalcone (NHDC), thaumatine, glycyrrhizin is increase the perception of sodium or calcium saccharinates saccharin, acesulfame, cyclamates etc. some taste suppressant and potentiates are given bellow.

Table no 17: Some taste suppressant and potentiators used for taste masking.

Drug	Category	Taste suppressant/ Potentiator used
Bromhexine	Mucolytic	Thaumatin and sugar
Caffeine	Diuretic	Hydroxyflavones
Paracetamol	Antipyretic	Potentiator: Glycyrrhizin, thaumatin and neohesperidine dihydrochalcone Sweeteners: Saccharin salt, acesufame.
Sugar alcohol	Nutritive agent	Aldehydes(Citral dimethyl acetal) and flavours
Pioglitazone	Anti-diabetics	Sodium chloride and coating with saccharides

i. Taste masking by gelatin[2]

Water insoluble gelation on the surface of tablet containing bitter drug can be used for the taste masking. The sodium alginate has the ability to cause water insoluble gelation is insoluble in presence of bivalent metal ion. Tablet of amiprolose hydrochloride have been taste masked by applying an undercoat of the sodium alginate and overcoat of calcium gluconate.

j. Salt formulation and derivatives

In this method attempt is made to modify the chemical composition of drug substances itself, so as to render it less soluble in saliva and thus make it less sensitive to the taste buds. The aspirin tablets can be rendered tasteless by making the magnesium salt of aspirin. D-Chlorpheniramine maleate is a taste masked salt of chlorpheniramine. The alkyloxy alkyl carbonate of clarithromycin have remarkably a nbitterness and improved bioavailability when administered.

k. Use amino Acid and Protein hydrolysates

By the combining of amino acid or salt with bitter drug, it is possible to substantially decrease the bitterness. Some of the preferred amino acid include sarcosine, taurine, alanine, glycine, and glutamic acid. The taste of ampicillin improve markedly by preparing it granules with glycine and mixing with additional quantity of glycine, sweeteners, flavors and finally compressing them into tablets.

l. Miscellaneous[3]

a. By effervescent agent

Effervescent agent has been shown to be useful and advantageous for oral administration of drug and have been employee for use as taste masking agent for dosage forms that are not dissolved in water prior to administration.

Table No 18: Example of effervescent agent method using taste masking.

Drug	Polymer	Result
Fexofenadine HCL	Sodium Bicarbonate	Fast dissolving tablet is formulate

b. pH modifier

pH modifying agent are able to generating a specific microenvironment in aqueous media that can be facilitate in- situ precipitation of the bitter drug substances in saliva there by decreasing the overall taste sensation for liquid dosage form is line suspension.

Table No 19: Example of pH modifier method using taste masking.

Drug	Modifier	Result
Des-quinolone	L-arginine	L-arginine is used to maintain the pH

c. Continuous multipurpose melt technology (CMT)

CMT method was mainly developed for continuous granulation and coating of the pharmacologically active substances. It was included in that method could be successfully applied for taste masking of bitter drug.

d. Wet Spherical Agglomeration:

The new microencapsulation method combined with wet spherical agglomeration method was used to mask the bitter taste of enoxacin.

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