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TASTE MASKING OF BITTER DRUGS BY USING ION EXCHANGE RESIN METHOD

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ABSTRACT

The various organoleptic properties such as taste, smell, texture also these are important factor in development of oral dosage forms. The taste is the major factor that affect the patient compliance and product quality. Acceptability of any dosage form mainly depends over its taste i.e. mouth feel. Drug molecule interact with taste receptor on the tongue to give bitter, sweet or other taste sensation, when they dissolve in saliva. The taste buds shows the sensation of taste by signal transduction from the receptor organs. Now a days most of the potent drugs that are cardiac, analgesic, anti-inflammatory, anti-tubercular, antibacterial, anthalmetics, antimalarial, antiepileptics, anticoagulants, histamine receptor agonist, antithyroids, antineoplastic, antiprotozoal, diuretics, nutritional agents, opioid analgesic, sex hormones, vaccines most of them are bitter in taste. So it become a necessary to develop such a dosage form that is acceptable for its taste by patients especially children or geriatrics. It becomes a challenge for pharmacist to make palatable formulation by masking the bitter taste of the drug.

KEYWORDS: Taste, taste buds, taste masking, ion exchange resin, taste masking technique, solid dispersion technique.

INTRODUCTION

Taste is the ability to detect the flavour of various substances like food, drug, etc. Taste is important factor governing the patient compliance. Acceptability of any dosage form mainly depends on its taste. Physiologically human can detect 4 kind of taste. Dosage form upon administration it dissolve in saliva and get interact with taste receptor to give taste sensation. The many active ingredients having bitter taste so pediatric patient generally fails to take medication properly. So masking of bitter taste becomes an essential part. To overcome such

a problem, many techniques have been developed to mask the bitter taste of drug, these are coating, inclusion complexes, microencapsulation, granulation, adsorption, prodrug approach, addition of flavours and sweeteners, ion exchange resin, etc.

Physiology of taste[1]

The sense of taste is medicated by taste bud, which are group of 50-100 cells of taste receptor that bundled together in cluster like bananas. They give sensation of taste with the help of sensory neuron to central nervous system in the brainstem. Upon ingestion chemical form medicament dissolve in saliva and chemoreceptors are stimulated, followed by interaction with surface protein gustducin that causing electrical changes within taste cells, which causes the transmission of signal to the brain.

Physiologically human can detect 4 types of taste

1. Salty taste:- They are found on the edge of upper front portion of the tongue.
2. Sweet taste:- They are located on tip of the tongue.
3. Bitter taste:- They are located at back of tongue.
4. Umami taste:- Certain amino acid having umami taste (eg. Glutamate, aspartate and related compound).

Taste signalling pathway

When tastant (eg. Medicine or food binds or interact with taste receptor taste transduction begins. The tastant bind with G- protein coupled receptor in the cell which triggering release of G-protein called gustducin.

The taste sensation process begins when Gustducin activate the effector enzyme phosphodiesterase (PDE) or phospholipase C beta-2 (PLC). Then there is changes in the intercellular level of second messenger such as cyclic adenosine monophosphate (cAMP), inositol 1,4,5-triphosphate (IP3), diacylglycerol (DAG). These sec. messenger activate ion channel including calcium channel inside the cell and sodium, potassium and calcium channels on extracellular membrane. This ionization causes the cell depolarization and release of neurotransmitters that send nerve to the brain, that carries the signal of bitter taste and taste blockers work by interfering with transduction.

Table: Specific area of tongue and threshold concentration for primary taste sensation

Taste	Area of tongue	Threshold concentration
Sweet (sucrose)	Tip	0.5
Salt (NaCl)	Tip and sides	0.25
Sour (HCl)	Sides	0.007
Bitter (quinine)	Back	0.00005

Ideal properties for taste masking process

1) Its nature should be physically and chemically inert.
2) It involve least no. of equipment and processing steps.
3) Excipients should be easily available and economical.
4) It should have high margin of safety.
5) It should have least manufacturing cost.
6) It should be rapid and easy to prepare.
7) It should be stable at room temperature.

Methods of taste masking

For elimination of bitter taste of orally administered pharmaceuticals various technique and strategies are adopted by pharmaceutical scientist. These are as below-

1) Addition of flavouring and sweetening agents.
2) Prodrug approach
3) Complexation with ion exchange resin
4) Inclusion complexation.
5) Multiple emulsion technique.
6) Taste masking by gelation
7) Bitterness inhibitor.
8) Polymer coating of drug
9) Solid dispersion
10) Development of liposome
11) Microencapsulation
12) Taste masking by adsorption
13) Taste making with lipophilic vehicles like lipids and lecithin
14) Taste suppressant and potentiators
15) Granulation
16) miscellaneous

Selection can be made based upon the type of drug, route of administration and compatibility of the active drug with suitable masking agent.

1) Addition of flavouring and sweetening agents

It is a common method of taste masking. But its use is limited to highly bitter actives. Nowadays both natural and synthetic sweeteners, flavours are available for the efficiency of these methods.

Sweeteners

Different grades of sweeteners are available in order to control the taste. The following table gives a compilation of most common artificial and natural sweeteners with their relative sweetness to sucrose and comments pertaining to each.

Table 1: Relative sweetness of commonly used sweeteners.[2,3]

Sweetening agents	Relative sweetness	Comment
Aspartame	200	Not very stable in solution
Acesulfame	137-200	Bitter after taste if used in higher concentration
Potassium 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

*sucrose is taken as a standard of 1 for comparison

Flavouring agent

Flavour is a complex effect of three components taste, odor and feeling factors. Suitable flavours are selected through taste panel studies. Most time blends of flavours were used to taste mask. Now since many flavours are odorous, the brain receives some additional impulses from the olfactory receptors in the nose which coordinate with the gustatory stimuli to produce the mingled sensation that is recognized as the flavour of a substance.

Flavouring agents may be classified as natural and synthetic. Various natural flavours like anise oil, cardamom, wild cherry, lemon, orange and peppermint are available. Various flavours are mentioned below:

Table 2: Shows various natural and artificial flavours.[4]

Type	Example	Significance
Natural	Peppermint	Less stable
Artificial	Vanilla	Highly stable
Natural and artificial	Strawberry	Effective at low concentrations

Natural and artificial flavours can generally be described to have taste masking effect. The table gives list of taste maskers with basic complementing taste.

Table 3: Shows agents for masking and complementing the basic taste.[5]

Basic taste	Masking agent
Sweet	Vanilla, bubble gum, grape
Acid	Lemon, lime, orange, cherry, grapefruit
Bitter	Liquorice, coffee, chocolate, mint, grapefruit, cherry, peach, raspberry, orange, lemon, lime.
Metallic	Berries, mints, grape, marshmallow, gurana.

Syrup of cinnamon, orange, citric acid, cherry, cocoa, wild cherry, raspberry, or glycyrrhizin elixir can be used to effectively mask salty and bitter tastes in a number of drug products. The cooling effect of some flavours aids in reducing after-taste perception. Eucalyptus oil is a major constituent of many mouth washes and cough syrup formulations. Menthol, chloroform and various salts are used as flavour adjuncts. They impart flavour and odour of their own to product and have a mild anaesthetic effect on sensory receptor orange associated with taste. Vitamins containing oral solutions are rendered bitterness free by adding sugar, amino acid and apple flavours. Oral composition containing vitamin B-complex, sodium 5-ribonucleotide (inosinate), citrus (orange) flavours or fruit flavours also have remarkably improved taste.

Table 4: Taste masking with flavours, sweeteners, amino acids.[6-17]

Drug/ active agent	Type of formulation	Taste masking agent
Eucalyptus oil	Mouthwash	Fenchone, bornel or isobornel
Benzethonium chloride	Dentifrices	Stevia-based sweeteners extracts and glycerine
Zinc acetate dehydrate	Lozenges	Anethol-beta-cyclodextrin complex and saccharin
Aspirin	Effervescent tablets	Sodium phenolate
Thymol	Oral rinses	Anethole, eucalyptol and methyl salicylate
Theophylline	Elixirs	Sodium saccharin, sodium glutamate and vanilla.
Chloropheniramine	Solution	Sodium bicarbonate, citric acid and orange flavour/cream flavour
Ibuprofen	Syrup	Sodium saccharin and refined sugar

Famotidine	Solution	Sodium bicarbonate, citric acid, lemon flavour.
Acetaminophen	Suspension	Sodium bicarbonate, citric acid and cherry flavours.
Guaifensin	Solution	Monosodium glycyrrhizinate
Caffeine	-	Starch, lactose and mannitol.
Anticholesterolemic saponins	-	Glycerine, alanine and flavours.

2) Prodrug approach

A prodrug is a chemically modified inert drug precursor which upon biotransformation liberates the pharmacologically active parent compound. By changing the molecular configuration of the parent molecule, the magnitude of a bitter taste response or taste receptor-substrate adsorption constant may be modified. Prodrugs can be used to increase or decrease the aqueous solubility, mask bitterness, increase lipophilicity, improve absorption, decrease local side effects, and alter membrane permeability of the parent molecule.

Table 5: Example of prodrugs with improved taste.[18-19]

Parent drug	Prodrug
Erythromycin	Erythromycin propionate
Clindamycin	Clindamycin palmitate ester
Chloramphenicol	Chloramphenicol palmitate ester
Morphine	N-oxide derivatives of all morphine
Triamcinolone	Triamcinolone diacetate ester
Gabapentin	Gabapentin XP13512
norfloxacin	Norfloxacin alkyl carbamates

3) Complexation with Ion exchange resin[20]

Ion exchange resin are the substance that are insoluble polymer containing acidic or basic functional group and having ability to exchange counterions within aqueous solution surrounding them. These ion exchange resins are insoluble matrix in form of smaller beads, usually white or yellowish, fabricated from an organic polymer backbone. The material have pores on the surface from where the ions are trapped or released. The ion trapping takes place only with simultaneous release of other ion, these process called ion exchange.

There are various types of ion exchange resin. They having many application due to their high separation capacity, fast ion exchange rate, good electrical conductivity. These resin are also used for various separation, purification and decontamination processes.

The most common example are water softening and water purification. Ion exchange resin having application not only as a drug carriers, but also in formulation and drug delivery and biomedical analysis. These resin are used for overcoming the formulation problems.

Including poor stability and poor dissolution, for taste masking and as a powder processing aid. These are used to modify the drug release the drug release from the formulation and are used substantially in oral, ophthalmic, nasal, transdermal, parentral drug delivery because of their diverse properties and application.

The ion exchange resin are based on cross-linked polystyrene. Cross-linking lowers the ion exchange capacity of the resin and extend the time needed to accomplish ion exchange processes. Particle size also shows influence on resin parameter, smaller the particle size larger outer surface, but causes larger heads loss in the column processes.

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 are 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:

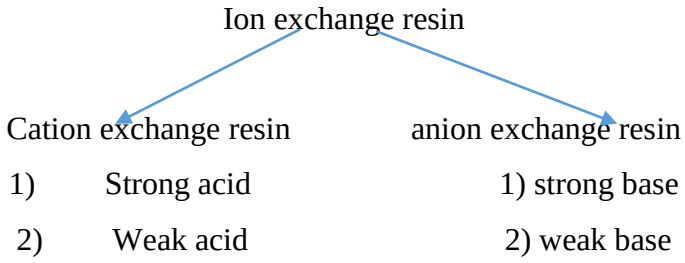

Figure: Classification of ion exchange resin.

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 resin 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 behave 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 deioinizing acidic metal finishing wastewater.

2. Anion exchange resin

These having exchangeable ion are negatively charged. These are firstly prepared by the chlormethylating 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- Resin+ -A- +ex-

Anion exchange resin can be classified as:-

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.

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.

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

Consequently, regeneration needs only to neutralize the absorbed acid; it need not provide OH ions. Less expensive weakly basic reagents such as ammonium (NH3) or sodium carbonate can be employed.

Properties of ion exchange resin:-

1. Cross- linking

The amount of cross-linking depends on the proportions of different monomers used in the polymerization step. Practical ranges are 4% to 16%. Resin with very low cross-linking tend to be watery and change diamension markedly depending on which ions are bound. Properties that are interrelated with cross-linking are:

Moisture Content

A physical property of the ion exchange resins that changes with changes in cross-linkage is the moisture content of the resin. For example, sulfonic acid groups ($-SO_3H$) attract water, and this water is tenaciously held each resin particle. The quaternary ammonium group of the anion resins also behave in a similar manner.

Capacity

The total capacity of an ion exchange resin is defined as the total number of chemical equivalents available for exchange per some unit weight or unit volume of resin. The capacity may be expressed in terms of milliequivalents per day gram of resin or in terms of milliequivalents per millilitre of wet resin.

The more highly cross-linked a resin, the more difficult it becomes to introduce additional functional groups. Sulfonation is carried out after the cross-linking has been completed and the sulfonic acid group ($-SO_3H$) are introduced inside the resin particle as well as over its surface. Likewise, the quaternary ammonium groups are introduced after the polymerization has been completed, and they too are introduced both inside the particle as well as on its surface. Fewer functional groups can be introduced inside the particles when they are highly cross- linked, and hence the total capacity on a dry basis drops slightly.

This situation is reversed when a wet volume basis is used to measure the capacity on a resin. Although fewer functional groups are introduced into a highly cross- linked resin, these groups are spaced closer together on a volume basis because the volume of water is reduced

by the additional cross- linking. Thus, the capacity on a wet volume basis increases as cross-linking increases.

Equilibration rate

Ion exchange reactions are reversible reactions with equilibrium conditions being different ions. Cross- linking has a definite influence on the time required for an ion to reach equilibrium. An ion exchange resin that is highly cross-linked is quite resistant to the diffusion of various ions through it, and hence, the time required to reach equilibrium is much longer.

2. Available capacity

The capacity of an ion exchange is a quantitative measure of its ability to take up exchangeable counter ions and it is therefore of major importance.

Acid-base strength

The acid or base strength of an exchanger is dependent on the various ionogenic groups incorporated into the resin. Resin-containing sulfonic, phosphoric and carboxylic acid exchanger group have approximate pKa values of < 1,2,3 and 4-6, respectively. Anionic exchanger are quaternary, tertiary, or secondary ammonium groups having apparent pKa values of >13,7-9 or 5-9, respectively. The pKa value of the resin will have a significant influence on the rate at which the drug will be released from resinate in the gastric fluids.

Selectivity of the resins for the counter-ion

Resin selectivity is attributed to many factors. Since ion exchange involve electrostatic forces, selectivity at first glance should depend mainly on the relative change and the ionic radius of the (hydrated) ion competing for an exchange site. The extent of adsorption increases with-

1. The counter ion that in addition to forming a normal ionic bond with the functional group of an exchanger, also interacts through the influence of van der Waal forces with the resin matrix.
2. The counter ion at least affected by complex formation with its co-ion or non-exchange ion.
3. The counter ions that induce the greater polarization. These factors, together with the effect of the size and charge of an ion on exhibiting certain selectivity toward a resin, are at best only general rules, and as a consequence there are many exceptions to them.

Preparation of resinate[21]

Two methods namely batch process and column process is employed for preparation of drug resinates. These two methods are as follows:

1) Batch process

In this process, an ion exchange resin is added to water in order to prepare its slurry. The accurately weighed amount of drug is then added to this slurry which is followed by stirring to prepare the complex. After the formation 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 the drug with resin.

2) Column process

In a typical column procedure the resin is slurried in water and added to a column and backwashed with water to eliminate air pockets and distribute the beads. Acid (0.1 N 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 adsorb a carboxylated drug on ion exchange resin, using NaOH to convert the resin to basic cycle.

The batch process is always preferred over column process in case of preparation of taste masked ion exchange resinates. The major reason behind this is the fine particle size of the ion exchange resin which does not allow them to be used in columnar operations due to chances of washing away during operations. Higher swelling efficiency in the batch process makes more surface area available for ion exchange.

Factors affecting ion exchange resin complexation

Following are the various factors that affect the process of ion exchange resin complexation and thereby needs special considerations.

Particle size and form

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

Porosity and swelling

Porosity affects the ability of ions to penetrate into resin matrix and thus the efficiency of complexation. The amount of cross-linking substance used in polymerization method

determines the porosity of resin. The amount of swelling is directly proportional to the number of hydrophilic functional group attached to the polymer matrix and is inversely proportional to the degree of DVB cross-linking present in the resin.

Cross- linking

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

Exchange capacity

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

Mixing time

The increase in mixing time enhances the swelling of resin which ultimately results in increased drug loading. Lower mixing time results in improper swelling and decreased percentage of drug complexation.

Effect of temperature

For certain resins the effect of temperature on drug loading has been reported. High temperature may also cause swelling of resin. Cation exchange resin doesn't get significantly affected by temperature changes unlike anion exchangers.

pKa

The pKa value of the resin is having significant influence on the rate at which the drug is released from the resinate in gastric fluids. The pKa of the drug also decides the extent of dissociation and complexation with the resin. If the pH is higher than pKa of drug, the drug remains mostly in nonionized form resulting in decreased complexation. At a certain pH, wherein, both the drug and the resin are ionized in sufficient quantity, resulted in maximum resinate formation.

Stability

At ordinary temperature and environmental conditions, the ion exchange resins are inert substance and resistant to decomposition through chemical attack. They get degraded and degenerated in presence of gamma rays.

Purity and toxicity

Resins are not absorbed by body tissue and are safe for human consumption careful purification of resins 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.

Application of ion exchange resin in various formulation related problems[20]

Taste –masking

Excessive bitterness of the active principal ingredients (APIs) oral formulations is the major taste problem faced by the pharmaceutical industry. Bitterness of formulations can influence selection by physicians and markedly affect patient compliance. Masking of the unpleasant taste of a drug improves compliance and product value. Amongst the numerous available taste-masking methods, ion exchange resins are inexpensive and can be used to develop a simple, rapid and cost-effective method of taste masking.

- Rapid dissolution
- Powder processing aid
- Stability
- Deliquescence
- Disintegration

Table 6: Example of drug masked by using ion exchange resin.[22]

Drug	Resin used	Matrix	Functional group	Standard ionic form
amphetamine	Ambrelite IRP 69	Styrene DVB	-SO3H	Na+
Propranolol HCL	Tulsion 344	Styrene DVB	-SO3H	Na+
dextromethorphan	Tulsion 344	Styrene DVB	-SO3H	Na+
Erythromycin stearate	Kyron-T 154	Styrene DVB	-SO3H	Na+

Table 7: List of commonly used ion exchange resin.[22,23,24,25,26,27,28,29]

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 8: Examples of drug masked with ion exchange resin with their exchange capacity.[30,31]

Drug	Resin	Matrix	Functional group	Standard ionic form	Exchange capacity
Spiramycin	Ambrelite IRP 64	Methacrylic	-COOH	H+	10meq/kg
Beta lactum antibiotics	Ambrelite IRP 88	Methacrylic	-COOH	K+	-
Norfloxacin	Tulsion 335	Methacrylic	-COOH	H+	10meq/kg
Paracetamol	Tulsion 339	Methacrylic	-COOH	H+	-
Cefuroxime axetil	Kyron T-104	Methacrylic	-COOH	H+	-
Tramadol HCl	Kyron T-114	Methacrylic	-COOH	H+	-
Roxithromycin	Indion 204	Methacrylic	-COOH	H+	10meq/kg
Azithromycin	Indion 234	Crosslinked polyacrylic	-COOH	K+	-

Table 9: Patent related taste masking composition including ion exchange resin.[32-51]

Patent No.	Drug	Inventor, year
WO2012/167878A1	Ketoprofen	LI Michael H.C., Kurmme M., 2012
WO2012/120522A1	Siladenafil	Murpani D., 2012
WO2011/080683A1	Anti-retroviral	Kakumanu V. K., Isloor S., Arora, 2011
WO2011/030351A2	Phosphodiesterase-5(PDE-5) inhibitors	Pilgaonkar P. et al. 2011
US2011/0300224A1	Escitalopram	Murpani D., Pandora A. 2011

US80088378B2	Active drug	Hargens R.D. et.al
WO2010/150221A1	Pregabilin	Huda I., et. Al. 2010
WO2009/074995A1	Sildenafil citrate	Singh S., et.al, 2009
US2008/0044371A1	Active drug	Hargens R.D. et.al, 2008
US2008/0095842A1	Levocitrizine dihydrochloride	Anterkar A.K., et.al, 2008
WO2007/146293A3	Active drug	Becicka B.T., et.al, 2007
US2006/0204559	Dextromethorphan	Bees W.S., et.al, 2006
US2006/0115529	Active drug	Jeong S., et.al., 2006
US2005/0036977	Active drug	Gole D., et.al., 2005
WO2005/013934A2	Active drug	Hergens R. D. et.al., 2005
US6,565,877,B1	Active drug	Mukhargi G, et.,al 2003
WO01/70194A1	Dextromethorphan	Bees W.S., et.al,2001
US5032393	Ranitidine	Douglas S.J. Bird F.R. 1991
EP0212641	Active Amino or amino group	Damani N.C., Tasu J.H.1998
US6,514,492B1	Quinolones	Gao R., et al 2001

Table 10: Patent related taste masking composition of polymer.[52-66]

Patent no.	Drug	Polymer	Inventor, Year
US8414919	Cimetidine, Ciprofloxacin	Amylose Starch	Gervais S. et al., 2013
WO/2012/063257	Active drug	Resin	Pilgaonkar P. et al, 2012
US8337890	Morphine, ibuprofen, Codeine	HPMC	Mehta K., Tu, Yuhsing, 2012
US8062667	Oxycodeine, Albuterol, Methylphenidate, Dextromethorphan	Ambrelite, IRP-69	Mehta K., Tu, Yushing
US20110136921	Venlafaxine HCl, Diclofenac sod.	HPMC K100M	Dumbre N.T., et al, 2011
WO/2010/127100	Pseudoephedrin, Chlorpheniramine, Hydrocodone	Ambrelite IRP-69	Mcbermott J. Joseph et al, 2010
USP20080118570	Chlorpheneramine, polistirex, sod. Polysterene sulfonate.	Ambrelite IRP-69	Liu Z, et al, 2008
USP20070128269	Chloroquine and pyrimethamine	HPMC K100M	Gervais S. et al, 2007
USP20060263431	Oxycodone, Meperidine, Methadone, Nalbulphire, Opium, Pentazocine.	Styrene-divinyl benzene	Maloney A. M., 2006
USP20050265955	Hydrocodone, bitartrate	Dowex 50 WX8H	Raman S.N. et al., 2005
WO/2003/020242	Dihydrocodeine phosphate, Codeine phosphate, Noscapine HCl	Ambrelite IR-120	Meadows D., et al
USP20020164373	Butorphanol, Fentanyl, Codeine, Dihydrocodeine	Hydroxyalkylcellulose/ SVB	Maloney A.M., 2002

USP6258350	Pilocarpine, Epinephrine	Poly(styrene-divinyl benzene)	Mallick S., 2001
USP5186930	Phenyl propenolemine	SVB	Kogan P.W., et al, 1993
EP0429732	Betaxolol, Befumolol	Ambrelite, dowex	Jani R. Hams R.G., 1991

Table 11: Examples of drug taste masked by ion exchange resins.[67]

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

3) Inclusion complex[3,68,69,70]

In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent i.e., the host molecule forming stable complex. The complexing agent is capable of masking the bitter taste of the 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.

Vander Waals forces are mainly involved in inclusion complexes. Beta-cyclodextrin is most widely used complexing agent for inclusion type complexes. It is sweet, nontoxic, cyclic oligosaccharide obtained from starch. The suppression of bitter taste cyclodextrin was in

increasing order of alpha, gamma, and beta cyclodextrin. Cyclodextrins (CDs) are cyclic oligosaccharides made up of six to twelve D-glucopyranose monomers connected at 1 and 4 carbon atoms. The αCD comprise 6, the βCD 7 and ɣCD 8 glucopyranose units.

Table 12: Taste masking by inclusion complex.

Drug	Polymer	Result
Primaquine phosphate	β cyclodextrin	Cachets prepared using physical mixture of drug and beta cyclodextrin in ratio of 1:25 showed complete bitter taste masking and easy redispersibility
Cetirizine dihydrochloride	α cyclodextrin, βcyclodextrin, ɣ cyclodextrin	β-CD is only recommendable CD for taste masking oral pharmaceutical formulations.
Cefuroxime axetil	βcyclodextrin	Inclusion complexation with βCD was found to be an excellent method in attaining palatability by masking undesirable taste of cefuroxime axetil.
Ibuprofen aqueous solution	Hydroxypropyl βcyclodextrin	Taste masking was achieved by weight ratio of ibuprofen: hydroxypropyl betacyclodextrin 1:11 to 1:15

4) Multiple emulsion[5,71]

A novel technique for taste masking of drugs, the w/o/w or o/w/o type multiple emulsions are vesicular systems in which active ingredients can be entrapped in internal phase. The entrapped substances can be transferred from internal phase to external phase through the 'membrane phase'. These phase controls the release of drug from system. Both w/o/w or o/w/o multiple emulsions of chloroquine phosphate have been prepared and reported to be partially effective in masking the bitter taste of drug.

5) Taste masking by gelation[72]

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

6) Bitterness inhibitors[72]

The development of a specific universal inhibitors for bitter taste has been widely required in the fields of taste physiology and pharmaceutical sciences, but no such inhibitors has been available. One difficulty in discovering of universal inhibitors for bitter taste is that

substances that inhibit bitterness of one compound will not influence the bitterness of a second because many different classes of compound impart bitterness.

7) Polymer coating of drug[73]

This is the simplest and most feasible option to achieve taste masking. The coating acts as a physical barrier to the drug particles, thereby minimizing interaction between the drug and taste buds. Coating of chewable tablets provides excellent taste masking while still providing acceptable bioavailability.

Table 13: Taste masking by polymer coating.

Drug/ active agents	Technique	Polymer used
Pinaverium bromide	coating	Cellulose or shellac
Propantheline bromide	coating	L-HPC, EC
ibuprofen	Air-suspension coating	Methacrylic acid copolymer (eudragit)
Triprolidine HCl	Dispersion coating	HPMC
dimenhydrinate	-	Eudragit or CMC or starch
Cefeanel daloxanate HCl	Granulation and coating	PVP, EC, HPMC, trisodium citrate
Enoxacin	Granulation and coating	HPC, HPMC, EC
Sparfloxacin	Granulation and coating	L-HPC, EC, HMC/EC, HPMC, titanium dioxide, and sucrose fatty acid ester mixture.
Ibuprofen	Rotogranulation and coating	HEC, HPMC
Aspirin	-	Cellulose acetate latex and triacetin
famotidine	Rotogranulation and coating	HPC, HPMC, cellulose acetate
Amoxycilline trihydrate	Granulation	MCC, L-HPC
Acetaminophen	Coating	Cellulose acetate, cellulose acetate butyrate, HPC/ cellulose acetate, Eudragit E100, PVP
Morphine HCl	Coating	Cellulose, Eudragit NE30D
Amiprilose HCl	Coating	Calcium gluconate and sodium alginate
Terfenadine	Mixing	Sodium alginate, carrageenan, macrogol-400
Beclamide	Microencapsulation	Gealtin
Clarithromycin	Rotogranulation	Carbopol, PVP
Roxithromycin	Granulation and coating	PEG, Eudragit L100-55
Nizatidine	Spray drying	Eudragit E100
Cetraxate HCl	Melt granulation,	Corn starch, macrogol-6000, Eudragit

	coating	S-100
Ciprofloxacin	Microencapsulation	Eudragit NE 30D, HPC
Ibuprofen	Spray coating	Eudragit L300, propylene glycol, mannitol and flavour
Bifemelane HCl	Coating and spraying	Glycerine monostearate, Eudragit L-30-D-55, PEG, sucrose
Cefuroxime axetil	Emulsion- solvent evaporation	Eudragit L-55 and RL
Pirenzepine and oxybutynin	Dispersion coating	Eudragit E-100, MCC, HPC
Diclofeanc	Microencapsulation	EC
Nicorandil	Coating	Crosscarmellose sodium, D-mannitol, lactose
Levofloxacin	Coating	Eudragit E100, Cellulose acetate

8) Solid dispersion technique[73]

They are dispersion of one or more active ingredient in an inert carrier or matrix in solid state, and insoluble or bland matrices may be used to mask the taste of bitter drug. Carrier used in dispersion system include povidone, polyethylene glycols, hydroxypropyl methylcellulose, urea, mannitol, ethylcellulose. Various approaches for preparation of solid dispersion are described below:

a) Melting method

In this method, the drug or drug mixture and a carrier are melted together by heating. The melted mixture is cooled and solidified rapidly in an ice bath with vigorous stirring. The final solid mass is crushed and pulverized.

b) Solvent method

In this method, the active drug and carrier are dissolved in a common solvent, followed by solvent evaporation and recovery of the solid dispersion.

c) Melting- solvent method

In this method, the drug in solution is incorporated into a molten mass of polyethylene glycol at a temperature below 70°C without removing the solvent.

Table 14: Taste masking by solid dispersion technique.[74,75,76,77,78,79,80,81,82,83,84,85]

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 HCl	Fast dissolving tablet	Solvent evaporation, Fusion method	Eudragit E100
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

9) By liposome formation[5,72]

Entrapment method of masking the obnoxious taste of therapeutic agent is to entrap them into liposomes. Liposomes are carrier molecules comprising lipids most often in spherical molecules with several layers of lipid, and the drug or biological agent is carried within the lipid molecules. Oils, surfactant, polyalcohols and lipids effectively increase the viscosity in the mouth due to which the decrease in contact between the bitter medicament and the taste receptors, thus improving the overall taste masking efficiency.

Table 15: Taste masking by liposomes formation.

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

10) Microencapsulation[3]

Microencapsulation is a process in which the active moiety (solid or liquid droplets) is coated with polymeric material or film. Coating the drug particles created a physical barrier between the drug and the taste buds and this taste of active could be masked. Microencapsulation is a valuable technique applicable to protect materials from volatilizing, oxidation as well as to mask their unpleasant taste.

pH independent water insoluble polymer have been used with enteric polymers, inorganic or organic pore formers to achieve taste masking by microencapsulation. Buffering agents are also included in suspending medium to increase taste masking efficiency of microcapsule in oral suspensions. Microecapsulation can be advantageous taste masking strategy for suspensions due to the low particle size distribution of microcapsules that can remain suspended for a longer time. The technique can be efficiently used for applying higher coating levels.

The following techniques are also used for microencapsulation

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

Table 16: Taste masking of bitter drugs by microencapsulation.

Drug	Technique	Polymer	Result
Ibuprofen	Air suspension coating	Methacrylic acid copolymer	Chewable taste masked tablet having controlled release characteristics by fluid bed coating, obtained.
Indeloxazine	Fluidized bed with side spray method	Hydrogenated oil and surfactant	Taste masking of drug without loss of bioavailability by heat treatment of wax coated microparticles.
Beclamide	Simple coacervation	Gelatin, anhydrous sodiumsulfate coacervating agent	Core: wall ratio 1:1, microencapsulation to mask bitter taste.
clarithromycin	Spray congealing	Amino alkyl methacrylate polymer E	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 into ODT.
Chloroquine diphosphate	Coacervation phase seperation	Ethyl cellulose	Taste masking achieved.

Table 17: Report on taste masking by microencapsulation.[19]

Drug	Category	Dosage form	Coating Material used
Acetaminophen	Antipyretic	Dispersible tablet	Cross carmallose
Caffeine/cimetidine	Diuretic/ Antihistamine	Chewable tablet	Eudragit RL30D, RS 30D
Ciprofloxacine	Floroquinolone antibiotics	Oily suspension	Eudragit NE 30D/RL 30D, HPMC
Levofloxacine	Floroquine antibiotic	Suspension	Eudragit E 100, Cellulose acetate.
Sildenafil citrate	Vasodilator		Eudragit NE 30D, E100
Chlorpheneramine maleate	Antihistamine	Mouth melt tablet	Ethyl cellulose
Dextromethorphan hydrobromide	Anti tissue		PVP-K30

Acetaminophen	Antipyretic	Chewable tablet	Eudragit E 100, Cellulose acetate.
Theophylline	Antipyretic	Dry suspension	Eudragit NE 30D, Guargum
Ampicillin trihydrate	Penicillins	Powders	Sodium CMC
Nizatidine	Antihistamine	Sprnkels	Eudragit E 100
Roxitromycin	Macrolides	suspension	Eudragit RS 100/ RL 100
Clarithromycin	Macrolides	powders	Glyceryl monosterate, Eudragit E 100
Chloroquine diphosphate	antimalerial	Powders	Eudragit RS 100
Metronidazole	Antiamoebic	Dry suspension	Eudragit E

11) Taste masking by adsorption[72]

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.

Adsorbate of bitter tasting drug can be considered as the less saliva soluble versions of these drugs. Adsorption involves preparing a solution of the drug and mixing it with an insoluble powder that will adsorb the drug, removing the solvent, drying the resultant powder, and then using this dried adsorbates in the preparation of the final dosage form. Many substrates like veegum, bentonite, silica gel and silicates can be used for the preparation of adsorbate of bitter drug.

Table 18: Taste masking by adsorption.

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

12) Taste masking by lipophilic vehicles[73]

Lipids

Oils, surfactants, polyalcohols, and lipids effectively increase the viscosity in the mouth and coat the taste buds, and therefore they are potential taste masking agents. Guaifenesin has improved taste when mixed with carnauba wax and magnesium aluminium silicate and then melt-granulated.

Lecithin and lecithin-like substances

Formulations with a large excess of lecithin or lecithin like substances are claimed to control bitter taste in pharmaceuticals. Magnesium aluminium silicate with soybean lecithin is used to mask the unpleasant taste of talampicillin HCl.

Table 19: Taste masking with lipophilic vehicle.

Drug	Technique/formulation	Taste masking agent
Guaifenesin	Melt granulation	Carnauba wax and magnesium aluminium silicate
Cimetidine	Granulation	Glyceryl monosterate
Gabapentin	coating	Gelatin and mixture of partially hydrogenated soybean oil and glyceryl monosterate
Isoprothiolane	Spray drying and coating	Hydrogenated oil and HPMC
Acetaminophen, diphenhydramine, carbetapentane citrate, noscapine HCl	syrup	Polyglycerine fatty acid ester, glycerine, and chained triglycerides
acetaminophen	Spraying/ tablet	Molten stearyl sterate
Quinine, L-leucine, iso-leucine, caffeine, and papaverine	-	Homogenated suspensions of phosphotidic acid and β-lactoglobulin
Talampicillin HCl	-	Magnesium aluminium silicate with soybean lecithin
Clarithromycin	-	Glyceryl monostearate and AMCE (amino alkyl methacrylate copolymer E)
Indeloxazine HCl	Fluidized bed drying	Hydrogenated oil and surfactants

13) Taste suppressant and potentiators[3]

Lipoproteins are universal bitter taste blockers. Study on animal model showed that lipoproteins composed of phosphatidic acid and lactoglobulin inhibit the taste nerve responses to the bitter substances without affecting those due to sugars, amino acids, salts or acid, potentiators increases the perception of the taste of sweeteners and mask the unpleasant after taste. Cooling and warming agents suppress unpleasant taste of medicament by subjecting taste receptors to extreme sensations to overpower the bitter taste and confuse the brain. A combination of cooling and warming agents was an effective alternative to achieve taste masking.

Table 20: Taste suppressants And Potentiators for taste masking.

Drug	Excipients	Result
Bromhexine	Thaumatin and sugar alcohol (e.g. erythritol and xylitol)	Masks bitter after-taste of Bromhexine
Caffeine	Hydroxy flavanones, their salts and stereoisomers	Suppressants do not have their own taste and work at even very low concentration.
Thymol	Cooling agent(e.g. methyl salicylate sweet and fruity compound) and sweet and herbaceous aromatic compounds.(e.g. anethole)	Mask taste of thymol without using a sugar alcohol.
Paracetamol	Potentiators: thaumatine, neohesperidine dihydrochalcone (NHDC), glycyrrhizin, and their mixtures.	Increase the sweetness. Perception (4 to 5 times) and mask the secondary taste of sweetening agents (metallic or bitter).

14) Granulation[86-100]

It is a less expensive, rapid operation and an easily scalable taste masking technology. Polymer, flavours and waxes have been used as granulating agents to achieve the taste masking of bitter medicaments. Liquid and low melting point waxes such as glycerol palmitostearate, glyceryl behenate and hydrogenated castor oil are commonly used ingredients during the granulation to achieve taste masking. Sugar alcohols and flavours are also added in the blend to increase the efficiency of taste masking. Both pH dependent and independent water insoluble polymers, especially the swelling polymers such as MCC and polycarbophil have been employed. During granulation, particle coating may remain incomplete. However, a swelling matrix phenomenon can reduce the overall diffusion of the bitter active. Thus, swellable polymers can give a better taste masking in granulation compared to non swellable polymers.

Table 21: Taste masking by granulation.

Granulating agent	Drug	Percentage of excipients	Comments
Sugar alcohol	Calcium containing compounds (e.g. CaCO3)	Concentration of sugar alcohol from about 5% to about 40%w/w	Melt granulation with sugar alcohol as the binding agent.
Alginic acid	Erythromycin	Drug:polymer ratio of 2:5:1 to 50:1	Taste masked granules, which can be formulated as dry syrup suspensions/chewable or dispersible tablets

Cyclodextrin	Dextromethorphan	Drug:polymer ratio of between 0.9:1 and 1:25	Mixing of drug with cyclodextrin followed by granulation; without complexation
pH dependent polymer (e.g. Eudragit E-100) and sugar solid support to coat drug-polymer mixture	Alprazolam	Drug-polymer mixture is 0.1 to 300% w/w relative to the weight of the solid support	Less expensive compared to coating
A neutral methacrylic acid ester copolymer and a binder	Norfloxacin	Polymer comprises 1 to 40% w/w of drug	Cost effective and environment friendly operations using aqueous solution
Polycarbophil	Macrolide antibiotic	-	-
Polacrillin potassium	Ondensetron	Polacrillin potassium 1 to 8% w/w and active pharmaceutical 1 to 10% w/w of final composition	Simple and economic process compared to freeze-drying
Microcrystalline cellulose	Ibuprofen	Ratio of drug to MCC is 70:30 to 90:10 w/w	A simpler and more effective process compared to coating
A water-swellable substance (hydroxypropyl cellulose, carmellose calcium or crosscarmellose sodium) with water or a hydrous alcohol	-	-	-
Flavours and a combination of a waxy material (e.g. glyceryl behenate or glycerol palmitostearate) and phospholipid (BMI-60) or an intense sweetener derived from fruit flavonoids	Granisetron hydrochloride	1 to 60 parts of medicament, 10 to 90 parts of xylitol, 0.5 to 20 parts of a waxy material, and 0.5 to 7 parts of an intense sweetener and/or taste masking agent	Cost effective with a rapid operation process

(neohesperidine)			
Wax- like material (e.g. hydrogenated castor oil) and sugar alcohol (e.g. erythritol)	Levofloxacin and clopidogrel sulfate	Ratio of drug to wax material is 1:1 to 1:5 w/w and sugar alcohol at least 10% w/w of the total composition	Suitable for administration to patient who have difficulty in swallowing compared to pH dependent water insoluble polymer or sugar (lactose) containing formulation that result in the clogging of syringe or tube
A polyglycerol ester of polyvalent fatty acid (rapeseed oil with hexaglycerol octastearate and tetraglycerol condensed ricinoleic acid ester)	Vitamin (a water-soluble)	Vitamin 1 to 70% w/w of the total composition and the degree of esterification of a polyglycerol ester of a polyvalent fatty acid is ≥70% with HLB value of ≤4.	-
An ester of glycerol or a fatty acid (e.g. glyceryl stearate) or a wax (e.g.besswax)	Telithromycin and pristinamycin	Drug and fatty acid present 15 to 30% and 60 to 80%w/w of the total composition respectively	Allows release of the active principle in acidic conditions
Hydrogel or a wax	Penicillin-based, cephem-based and macrolide- based antibiotics	-	-

- Shows lack of information due to limited details of New Zealand, Chinese and Japanese patents/ patent applications: only abstracts are available.

15) Miscellanous[72]

- **Viscosity enhancer**

Suspending coated particles may not be efficient enough to achieve taste masking of highly bitter medicaments in liquid orals. Usage of viscosity enhancers in these cases would retard the migration of dissolved medicament from the surface of the solid particle to the suspending medium.

Table 22: Taste masking by viscosity enhancer.

Drug	Viscosity enhancer	Result
Azelastine	Hypromellose	Taste mask achieved

- **pH modifiers**

pH modifying agents are capable of generating a specific microenvironment in aqueous media that can facilitate in-situ precipitation of the bitter drug substance in saliva thereby reducing the overall taste sensation for liquid dosage form is like suspension.

Table 23: Taste masking by pH modifiers.

Drug	pH modifier agent	Result
Des-quinolone	L-arginine	L-arginine is used to maintain pH

- **By using effervescent agents**

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have been employed for use as taste masking agents for dosage forms that are not dissolved in water prior to administration.

Table 24: Taste masking by effervescent agents.

Drug	Effervescent agent	Result
Fexofenedine HCl	Sodium bicarbonate	Fast dissolved tablet was prepared

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