Drug Development and Industrial Pharmacy

ISSN: 0363-9045 (Print) 1520-5762 (Online) Journal homepage: https://www.tandfonline.com/loi/iddi20

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To cite this article: Harmik Sohi, Yasmin Sultana & Roop K. Khar (2004) Taste Masking Technologies in Oral Pharmaceuticals: Recent Developments and Approaches, Drug Development and Industrial Pharmacy, 30:5, 429-448, DOI: 10.1081/DDC-120037477

To link to this article: https://doi.org/10.1081/DDC-120037477

Published online: 25 May 2004.

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DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 30, No. 5, pp. 429–448, 2004

REVIEW

Taste Masking Technologies in Oral Pharmaceuticals: Recent Developments and Approaches

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ABSTRACT

Taste is one of the most important parameters governing patient compliance. Undesirable taste is one of several important formulation problems that are encountered with certain drugs. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients. Several oral pharmaceuticals, numerous food and beverage products, and bulking agents have unpleasant, bitter-tasting components. So, any pharmaceutical formulation with a pleasing taste would definitely be preferred over a competitor's product and would translate into better compliance and therapeutic value for the patient and more business and profits for the company. The desire of improved palatability in these products has prompted the development of numerous formulations with improved performance and acceptability. This article reviews the earlier applications and methodologies of taste masking and discusses the most recent developments and approaches of bitterness reduction and inhibition for oral pharmaceuticals.

Key Words: Taste; Taste masking; Oral pharmaceuticals.

INTRODUCTION

The term ''flavor'' is used to describe the taste of any particular food or drink[1] and the sensation of taste, a chemical sense, can be expressed as a feeling by an individual when something is put into the mouth in order to ascertain the wholesomeness of the component. Four fundamental sensations of taste have been described:

- Sweet and salty, mainly at the tip.
- Sour, at the sides.
- Bitter, at the back.

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DOI: 10.1081/DDC-120037477
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Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist. The ideal solution to reduce or inhibit bitterness is the discovery of a universal inhibitor of all bitter tasting substances that does not affect the other taste modalities such as sweetness or saltiness. Two comprehensive reviews to control bitter taste have already been presented along with thoughts on the discovery of a universal bitterness inhibitor.[2,3]

GENERAL TASTE MASKING PRACTICES IN ORAL PHARMACEUTICALS

Bitterness reduction and inhibition are important characteristics of a good oral dosage form. Considerable amount of progress has been achieved in the development of taste-masked formulations in recent years. Proven methods for bitterness reduction and inhibition have resulted in improved palatability of these formulations.[4] Development of oral pharmaceuticals as replacements for normally injectable peptides may become increasingly common if reduced bitterness can be accomplished to a certain extent. An appreciable amount of success has been achieved in the development of bitterless, tasteless, and taste-masked formulations in recent years. Various techniques available for masking bitter taste of drugs include taste masking with ingredients such as flavors, sweeteners, and amino acids; taste masking by polymer coating; taste masking by conventional granulation; taste masking with ion-exchange resins; taste masking by spray congealing with lipids; taste masking by formation of inclusion complexes with cyclodextrins; taste masking by the freeze-drying process; taste masking by making multiple emulsions; and taste masking with gelatin, gelatinized starch, liposomes, lecithins or lecithin-like substances, surfactants, salts, or polymeric membranes.

Taste Masking with Flavors, Sweeteners, and Amino Acids

This technique is the foremost and the simplest approach for taste masking, especially in the case of pediatric formulations, chewable tablets, and liquid formulations. But this approach is not very successful for highly bitter and highly water soluble drugs. Artificial sweeteners and flavors are generally being used along with other taste-masking techniques to improve the efficiency of these techniques. Numerous pharmaceuticals such as dentifrices and mouthwashes applied to the oral cavity elicit unpleasant taste perceptions.[5] The unpleasant taste of certain formulations like mouthwashes and cough drops containing medicinal and bitter tasting substances such as eucalyptus oil can be masked by adding fenchone, borneol, or isoborneol. These taste masking agents significantly suppress the perception of unpleasant organoleptic sensations of the volatile oil.[6] The cooling effect of the taste masking agents also aids in reducing the bitterness. Sweetening compositions of di-D-fructofuranose 1,2′:2,3′-di-anhydride are also useful for dentifrices, mouthwashes, and foods. Menthol reduces the bitter taste, and low-calorie formulations show beneficial anticaries effects.[7] Nonbitter dentifrices are prepared by sweetening benzethonium chloride with stevia-based sweetener extract and glycerin. It exhibits 100% bactericidal activity against *E. coli*.[8] Anethole and menthofuran in various dentifrices are not only used to mask the bitterness but also to improve the low temperature stability of the formulation.[9] The use of some imitation flavors for masking the taste of ammonium chloride and other saline drugs has also been established. The various imitation flavor concentrates used are grape, maple, raspberry, and wild cherry, etc. These have been compared to some of the official flavored syrups and recognized as good masking agents for saline drugs.[10]

The bitter taste of zinc acetate dihydrate in lozenge formulations can be masked by using saccharin, anethol-β-cyclodextrin complex, and magnesium stearate followed by tableting with compressible polyethylene glycol and fructose.[11] Incorporation of anesthetizing agents such as sodium phenolate to an aspirin-medicated floss serves to numb the taste buds sufficiently for 4–5 seconds, rendering the bitter taste of aspirin imperceptible.[12] The combination of citric acid and sodium bicarbonate with certain flavors is used to mask the bitter taste of chlorpheniramine maleate and pheylpropanolamine HCl (orange flavor and cream flavor),[13] famotidine (lemon flavor),[14] and acetaminophen (cherry flavor).[15] Alkali metal carbonates and bicarbonates in combination with mint flavor, aniseed flavor, and sweeteners are used to improve the taste of diclofenac.[16] Glycyrrhiza and xanthan gum are used to improve the taste of extract containing pogostemi herba.[17] Monosodium glycyrrhizinate together with flavors has been used to mask the bitter taste of guaifenesin.[18] Clove oil has been found to be a good taste-masking component to mask the bitter taste of a number of medicinals, particularly analgesics, expectorants, antitussives, decongestants, or

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their combination because of its spicy and slight anesthetic effect. To support the taste masking capabilities of clove, honey vanilla or artificial vanilla flavor is preferred. Calcium carbonate, citric acid, or sodium bicarbonate may be included in the formulation if effervescence is required. Drugs, which can be taste masked by this composition, include acetaminophen, aspirin, ketoprofen, H_2-blockers, etc.[19]

A composition comprising of anethole, eucalyptol (provides cooling, vapor action), and methyl salicylate (inhibits bitterness) can be used to mask the unpleasant taste of thymol, leaving the consumer with a pleasant taste perception.[20] Sodium citrate dihydrate, sodium saccharin, refined sugar, and flavors have been used to mask the bitter taste of ibuprofen when formulated as a syrup with pyridoxine HCl.[21] Liposome-associated flavorents have been reported to mask the bitter taste of pharmaceuticals in aqueous suspensions.[22]

Aspartame is used as a prominent sweetener in providing bitterness reduction. A very small concentration (0.8%) is effective in reducing the bitterness of 25% acetaminophen. Starch, lactose, and mannitol have also exhibited taste-masking properties of caffeine.[23] Artificial sweeteners such as neohesperidine dihydrochalcone and hesperidine dihydrochalcone 4′-β-D glucoside have the ability to mask bitterness and saltiness by virtue of their lingering sweetness. A lingering sweetness provides taste masking, primarily because the taste profile of a bitter substance appears later in time than normal sugar sweetness generally lasts.[24] Low levels of monoammonium glycyrrhizinate are reported to mask the bitter, harsh, and astringent taste in chewable multivitamins, cough/cold syrups, oral antibiotics, chewable analgesics, and alcohol-based oral antiseptics. Several tasteless/sweetness inhibitors are being actively pursued as bitterness inhibitors. Lactisole, a sweetness inhibitor, possesses great potential in the taste masking of pharmaceuticals.[25]

Anticholesterolemic saponin-containing foods, beverages, and pharmaceuticals are supplemented with amino acids (such as glycine and alanine) and flavors for bitterness control.[26] Proteinlike compositions, useful for improvement of liver disorders, severe burns, trauma, etc., having branched amino acid-modified proteins, are tasteless and odorless.[27] Vitamin B oral solutions containing sugars, amino acids, and apple flavor are free from bitterness. Oral liquid compositions consisting of vitamin B, sod-5′-ribonucleoside (inosinate), and orange or fruit flavor also have improved taste.[28] Oral liquid compositions containing theophylline salts are

Table 1. Taste masking with flavors, sweeteners, and amino acids.

S. No.	Drug(s)/active agent(s)	Type of formulation	Taste masking agent(s)	Ref.
1	Eucalyptus oil	Mouthwashes/ cough drops	Fenchone, borneol or isoborneol	[6]
2	Benzethonium chloride	Dentifrices	Stevia-based sweetener extract and glycerin	[8]
3	Zinc acetate dihydrate	Lozenges	Anethol-β-cyclodextrin complex and saccharin	[11]
4	Aspirin	Medicated floss	Sodium phenolate	[12]
5	Thymol	–	Anethole, eucalyptol, and methyl salicylate	[20]
6	Ibuprofen	Syrup	Sodium citrate dihydrate, sodium saccharin, and refined sugar	[21]
7	Theophylline	Solution	D-sorbitol, sodium saccharin, sodium glutamate, and vanilla essence	[29]
8	Chlorpheniramine, Pheylpropanolamine	–	Sodium bicarbonate, citric acid, and orange/cream flavor	[13]
9	Famotidine	–	Sodium bicarbonate, citric acid, and lemon flavor	[14]
10	Acetaminophen	–	Sodium bicarbonate, citric acid, and cherry flavor	[15]
11	Guaifenesin	–	Monosodium glycyrrhizinate	[18]
12	Caffeine	–	Starch, lactose, and mannitol	[23]
13	Anticholesterolemic saponins	–	Glycine, alanine, and flavors	[26]

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formulated with D-sorbitol, sodium saccharin, sodium glutamate, and vanilla essence to produce a solution that is less bitter than a theophylline solution.[29] Table 1 summarizes taste masking of various drugs by flavors, sweeteners, and amino acids.

Taste Masking with Lipophilic Vehicles

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.[30] The taste of cimetidine can be improved by granulating it with glyceryl monostearate.[31] Gabapentin (acyclic amino acid, a drug for seizures) has improved taste when coated with gelatin and then mixed with partially hydrogenated soybean oil and glyceryl monostearate.[32] The taste of isoprothiolane can be masked by mixing it with hydrogenated oil at 80°C and spray dried. The resulting granules are coated with hydroxypropyl methylcellulose.[33]

Acetaminophen granules are sprayed with molten stearyl stearate, mixed with suitable tablet excipients, and incorporated into a taste-masked, chewable tablet formulation.[34] Bitterness-free syrup of carbetapentanecitrate, diphenhydramine HCl acetaminophen, and Noscapine HCl can be formulated using polygylcerine fatty acid ester, glycerin, and chained triglycerides.[35]

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 aluminum silicate with soybean lecithin is used to mask the unpleasant taste of talampicillin HCl. The drug is dissolved in or dispersed into an organic solvent such as chloroform. Lecithin is added to the solution or dispersion of the drug with stirring to give a blend. The blend is mixed with powdery excipients (e.g., magnesium aluminate metasilicate, synthetic aluminum silicate, lactose, mannitol, etc.), dried and granulated to give a taste-masked composition.[36] Homogenated suspensions of phosphatidic acid and β-lacto globulin from soybeans and milk, respectively, completely suppress bitter stimulants such as quinine, L-leucine, iso-leucine, caffeine, and papaverine HCl. More importantly, the suspension does not suppress sweet, sour, or salty taste.[37] Table 2 summarizes taste masking of various drugs with lipophilic vehicles.

Table 2. Taste masking with lipophilic vehicles.

S. No.	Drug(s)/active agent(s)	Technique/formulation	Taste masking agent(s)	Ref.
1	Guaifenesin	Melt granulation	Carnauba wax and magnesium aluminium silicate	[30]
2	Cimetidine	Granulation	Glyceryl monostearate	[31]
3	Gabapentin	Coating	Gelatin and mixture of partially hydrogenated soybean oil and glyceryl monostearate	[32]
4	Isoprothiolane	Spray drying and coating	Hydrogenated oil and HPMC	[33]
5	Acetaminophen	Spraying/tablet	Molten stearyl stearate	[34]
6	Acetaminophen, diphenhydramine, carbetapentane citrate, and noscapine HCl	Syrup	Polygylcerine fatty acid ester, glycerin, and chained triglyecrides	[35]
7	Quinine, L-leucine, iso-leucine, caffeine, and papaverine	–	Homogenated suspensions of phosphatidic acid and β-lactoglobulin	[37]
8	Talampicillin HCl	–	Magnesium aluminum silicate with soybean lecithin	[38]
9	Clarithromycin		Glyceryl monostearate and AMCE	[108]
10	Indeloxazine HCl	Fluidized bed drying	Hydrogenated oil and surfactants	[113]

Note: HPMC, Hydroxypropyl methyl cellulose; AMCE, aminoalkyl methacrylate copolymer E.

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Taste Masking by Coating with Hydrophilic Vehicles

This is the simplest and most feasible option to achieve taste masking. The coating acts as a physical barrier to the drug particles, thereby minimizing interaction between the drug and taste buds. Coating of chewable tablets provides excellent taste masking while still providing acceptable bioavailability. A specialized technique, i.e., micro emulsion technology, has been used for taste masking of powders, chewable tablets, and liquid suspensions.

Carbohydrates (Cellulose)

The taste of orally administered drugs can be masked by coating the drug with carbohydrates. Bitter solid drugs such as pinaverium bromide, a spasmolytic, has no bitter taste when formulated in an organoleptically acceptable manner by polymer coating with a mixture of cellulose or shellac and a second film-forming polymer soluble at pH less than 5.[38] A preparation of the antiulcerative drug propantheline bromide is coated on low substituted spherical hydroxypropyl cellulose and further coated with ethyl cellulose to mask the unpleasant taste while readily releasing the active ingredients.[38] Taste masking of ibuprofen has been successfully achieved by using the air-suspension coating technique to form microcapsules, which comprise a pharmaceutical core of crystalline ibuprofen and a methacrylic acid copolymer (Eudragit) coating that provides chewable taste-masked characteristics.[39]

An antihistaminic agent, chlorpheniramine maleate, has improved taste and palatability when an aqueous solution of 50 parts of the drug was absorbed into 3000 parts of Avicel PH101 (polymeric carbohydrate). The resultant mixture was finally spray coated with an aqueous solution containing xylitol to seal the polymeric pores.[40] The unpleasant taste of an antihistaminic agent, triprolidine HCl, can be masked with a dispersion coating of hydroxypropyl methylcellulose, a plasticizing agent, a sweetener, and a flavoring agent.[41] Various oriental drugs can be taste masked with celluloses and/or starches containing carboxymethyl (CM) groups. Examples include carboxymethyl cellulose (CMC), sodium CMC, and sodium CM starch.[42] Cross carmellose sodium has been used to mask the bitter tasting active agents and to impart rapid disintegrating properties to the tablet.[43] Dimenhydrinate (for motion sickness) has improved taste when coated with methacrylic acid copolymer (Eudragit) or carboxymethyl cellulose or starch and is available in a chewable tablet formulation. Alternatively, a delayed release matrix in an effervescent form of disintegrating tablets or instant granulates is also available. The drug containing matrix is applied to a carrier with fatty acid esters to provide taste masking.[44]

Core elements of drugs coated with a water-insoluble polymer such as ethyl cellulose offer taste masking and reduced dissolution profiles for a variety of drugs, including paracetamol, ranitidine HCl, doxycycline HCl, pseudoephedrine HCl, sodium naproxen, theophylline, and aspirin.[45] Pharmaceutical granules with bitter taste are coated with water-soluble polymers of hydroxypropyl methylcellulose and sugars such as sucrose and lactose to decrease the bitter perception at the time of administration.[46] The bitter taste of basic pharmaceutical salts can be reduced or masked with weakly alkaline compounds of good bioavailability. Cefeanel daloxate HCl, lactose, and corn starch were mixed and granulated with ethanolic solution of polyvinyl pyrollidone to produce granules. The granules were first coated with ethyl cellulose containing methylene chloride-methanol mixed solution. They were further coated with a similar solution of trisodium citrate and ethyl cellulose and then mixed with lemon oil and granules prepared from sodium saccharine, sucrose, and 2% hydroxypropyl cellulose aqueous solution. There was good bioavailability and no bitterness to volunteers.[47,48] Enoxacin was granulated with hydroxypropyl cellulose and hydroxypropyl methylcellulose and then coated with a mixture of ethyl cellulose and hydroxypropyl methylcellulose to produce a bitterness-free formulation.[49] Sparfloxacin (a quinolone antibacterial) is optimally taste masked by preparing film-coated granules. Higher levels of ethyl cellulose reduce bitterness most effectively. Optimal bioavailability is achieved with 20% drug, 52% low substituted hydroxypropyl cellulose (L-HPC) in the cores, and 10% ethyl cellulose (four parts), and hydroxymethyl cellulose (two parts) in the coating film.[50] The same drug can also be taste masked by coating with ethyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, and sucrose fatty acid ester mixture (4:2:1:1).[51]

The unpleasant taste of ibuprofen can be masked by making a suspension of the drug using the combination of primary suspending agents (xanthan gum/sodium carboxymethyl cellulose/microcrystalline cellulose/polysorbate 80). The composition is taste masked by primary taste-masking agents (sucrose/sorbitol/glycerin) and also contains a buffer acid (citric acid/phosphoric acid) to adjust the pH of the suspension between 1.5 to 4.1.[52] The same drug can also be formulated, rotogranulated, and coated with a

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solution containing hydroxyethyl cellulose and hydroxypropyl methylcellulose in water. The taste-masked granules are compressed into chewable tablets.[53]

Aspirin tablets can be taste masked with a plasticized thin film of cellulose acetate latex and triacetin at not more than 1% of the coated medicament.[54] A chewable tablet of famotidine was prepared using hydroxypropyl methylcellulose and lactose, rotogranulated, and coated with 10% solution of cellulose acetate and hydroxypropyl cellulose (70:30) in a mixture of 80:20 acetone and menthol.[55] The bitter taste of amoxycillin trihydrate was masked by mixing it with microcrystalline cellulose and granulating. The granules were further mixed with microcrystalline cellulose and hydroxypropyl cellulose (L-HPC) and tableted.[56] A chewable tablet of acetaminophen was prepared by compressing the coated particles. Particles are coated with a blend of cellulose acetate, cellulose acetate butyrate, and hydroxypropyl cellulose[57] or with cellulose acetate (39.8% acetylation); Eudragit E 100; and polyvinyl pyrollidone.[58] The coating provides excellent taste masking while still permitting acceptable bioavailability. The bitter taste of morphine hydrochloride can be masked by first coating it on spherical cellulose and then with an aqueous solution containing Eudragit NE 30D and talc. The particles were finally overcoated with Avicel RC-59INF, sucrose, D-sorbitol, sodium saccharin, methylparaben, and vanilla essence to produce powders with good sustained-release properties in water suspensions at pH 1.2–6.8 with no bitter taste.[59]

Proteins, Gelatins, and Prolamines (Zein)

Various forms of proteins have been used extensively for taste masking. Prolamine forms the main protein components of cereal grains and flour, and can be extracted from the flour with 80% alcohol, unlike other proteins. Most important prolamines are zein, gliadin, and hordein. Various antibiotics, vitamins, dietary fibers, analgesics, enzymes, and hormones have been effectively taste masked using prolamine coatings. The taste masking is effective over a prolonged storage period. Besides effectively masking the taste of the bitter drug, prolamine coating does not affect the immediate bioavailability of the active substance. Zein or gliadin in combination with plasticizer were highly effective in controlling the release of the active substance from the encapsulated particle and masking the unpleasant taste of the coated active substance.[60] Tylenol Geltabs that use the geltin-coating process offer ease of swallowing and taste masking. The notable disadvantage of this preparation is poor stability in hot and humid climates.[61] Hydrolyzed gelatin has been found to provide an improvement in taste and mouthfeel when incorporated into small amounts in chewable tablets containing ingredients for taste masking. There is large improvement particularly in the taste and mouthfeel of the chewables incorporating magaldrate and/or calcium carbonate.[62] For mint-flavored oral pharmaceutical gums, incorporating a prolamine/cellulose ingredient of high pH can reduce bitterness of flavor.[63] Water insoluble gels formed by sodium alginate in the presence of bivalent metals are also exploited for their taste-masking properties. Amiprilose HCl was taste masked by first coating the drug with calcium gluconate followed by a coating of sodium alginate. Upon oral administration, it forms a gel on the surface of the tablet to mask its bitter taste.[64] Terfenadine mixed with sodium alginate, carrageenan, and macrogol-400 gives a taste-masked formulation.[65] Ibuprofen and sodium alginate mixed in water and added dropwise to an aqueous solution of calcium chloride gives a tasteless and odorless jelly.[66] A gel base confectionary of acetaminophen was developed in order to improve children's compliance in taking the bitter medicine. The gel immediately changes into a jelly after adding a special liquid. It was reported that the bitter taste was completely disappeared in the jelly-formed medication.[67] The unpleasant taste of an antiepileptic drug, beclamide, can be masked by microencapsulation followed by tableting. Microencapsulation was performed using a simple coacervation method using gelatin. Anhydrated sodium sulfate was used as the coaceravating agent.[68] Cross-linked gelatin via glutaraldehyde and Eudragit resin L100-, S100-, and E100-coated microcapsules were effective in masking the bitter taste of clarithromycin and preventing its release under simulated storage conditions.[69] The bitter taste of clarithromycin can also be masked by granulating it with carbopol followed by rotogranulation with polyvinyl pyrollidone (PVP) solution.[70] The antidiarrheal agent loperamide or its salt can be taste masked by blending it with water soluble saccharides or starches, cellulose, and water insoluble metal salt or its acid followed by applying a sugar or film coating.[71] The antibacterial drug roxithromycin has improved taste when mixed with polyethylene glycol and water, granulated, dried, and then coated with an aqueous mixture of Eudragit L 100-55, sodium hydroxide, talc, triethyl citrate, and licorice flavor.[72] The same drug can also be taste masked by mixing it with Eudragit RS-100 in methylene chloride followed by spray drying.[73] Nizatidine has improved taste when mixed with Eudragit E-100 in ethanol/water (80:20) and spray dried.[74]

Melt granulation with water-soluble substances successfully reduces the bitterness of cetraxate and

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ofloxacin. Granules consisting of cetraxate hydrochloride, corn starch, and Macrogol-6000 were coated with a mixture of Eudragit S-100, talc, and silica to mask bitter taste.[75,76] Antibacterial quinolinecarboxylic acid derivatives, such as ciprofloxacin, are loaded on weak cation exchangers and administered to animals in their feed. The taste is improved as judged by the animals accepting the material more readily.[77] The bitter taste of ciprofloxacin can also be masked by microencapsulating it into a mixture of esters or quaternary ammonium salt of Eudragit NE 30D and hydroxypropyl cellulose.[78]

Remoxipride, a D2-dopamine receptor antagonist, is well tolerated and completely absorbed after oral administration. Because of its extremely bitter taste, remoxipride is not a good candidate for oral administration. So, a palatable oral suspension of the drug was developed using microencapsulation, which provides complete bioavailability, but has a delayed absorption rate of 3 h. In comparison, absorption was delayed only 1.6 h in a capsule form and only 1.0 h in an aqueous solution of 0.5% sodium lauryl sulfate.[79] Ibuprofen is encapsulated with a chewable methacrylic acid copolymer to reduce bitterness. A fluidized bed of ibuprofen crystals was spray coated with an aqueous dispersion of Eudragit L300 coating polymer, propylene glycol as plasticizer, and talc. The encapsulated ibuprofen was mixed with mannitol and flavor and compressed into tablets.[80]

Bifemelane HCl has been formulated as ''dry syrup'' to reduce bitterness. The drug is kneaded, circulated, coated with glycerin monostearate, and overcoated with Eudragit L30-D-55, polyethylene glycol, and talc. The mixture is then sprayed with sucrose to produce nonbitter dry syrup.[81] The bitter taste of diazepines can be masked by spray coating the drug with water-soluble (hydroxypropyl cellulose) and/or water-insoluble (amino alkyl methacrylate copolymer) polymers. A mixture of the coated drug particles, lactose, sucrose, mannitol, and corn starch was granulated while spraying with an aqueous hydroxypropyl cellulose solution.[82]

Zeolites

Bactericidal feeds for domestic animals generally impart bitter taste to the formulation and may create feeding aversion among the animals during the treatment. To improve the taste of such formulations, the active agent (tiamulin fumarate) may be dissolved in methanol, supported on mordenite-type zeolite or starch, dried, and further premixed with the supports to produce sustained-release, bitterness-free granules. The resulting formulation has stronger bactericidal effect on *Mycoplasma*, *Staphylococcus*, and *Corynebacterium*.[83] Table 3 summarizes taste masking of drugs by polymer coating.

Taste Masking by Inclusion Complexation

In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent, i.e., the host molecule, forming a stable complex. The complexing agent is capable of masking the bitter taste of drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds, thereby reducing the perception of bitter taste. This method is most suitable only for low dose drugs. Vander Waals forces are mainly involved in inclusion complexes.[64] β-cyclodextrin is the most widely used complexing agent for inclusion type complexes. It is a sweet, nontoxic, cyclic oligosaccharide obtained from starch.

The strong bitter taste of carbetapentane citrate syrup was reduced to approximately 50% by preparing a 1:1 complex with cyclodextrin.[84] Palatable ibuprofen solutions are prepared by forming a 1:11 to 1:15 inclusion complex with ibuprofen and hydroxypropyl β-cyclodextrin, respectively. The complex masked the bitter component but created a sore taste that was masked by sweeteners.[85] The unpleasant taste of pharmaceuticals or food additives containing gymnema sylvestre, a bitter and astringent tasting sweetener for diabetes control, can be masked by mixing with β-cyclodextrin. Besides masking its bitter taste, β-cyclodextrin further enhances the blood sugar lowering effects of gymnemic acids.[86]

Taste Masking by Ion-Exchange Resins (IERs)

Ion-exchange resins (IERs) are high molecular weight polymers with cationic and anionic functional groups. The most frequently employed polymeric network is a copolymer of styrene and divinylbezene. Ion-exchange resins are used in drug formulations to stabilize the sensitive components, sustain release of the drug, disintegrate tablets, and mask taste. Drug can be bound to the resin by either repeated exposure of the resin to the drug in a chromate graphic column or by prolonged contact of resin with the drug solution. Drugs are attached to the oppositely charged resin substrate, forming insoluble adsorbates or resinates through weak ionic bonding so that dissociation of the drug-resin complex does not occur under the salivary

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Table 3. Taste masking by polymer coating.

S. No.	Drug(s)/active agent(s)	Technique	Polymer(s) used	Ref.
1	Pinaverium bromide	Coating	Cellulose or shellac	[38]
2	Propantheline bromide	Coating	L-HPC, EC	[38]
3	Ibuprofen	Air-suspension coating	Methacrylic acid copolymer (Eudragit)	[39]
4	Triprolidine HCl	Dispersion coating	HPMC	[41]
5	Dimenhydrinate	–	Eudragit or CMC or starch	[44]
6	Cefeanel daloxate HCl	Granulation and coating	PVP, EC, HPMC, trisodium citrate	[48]
7	Enoxacin	Granulation and coating	HPC, HPMC, EC	[49]
8	Sparfloxacin	Granulation and coating	L-HPC, EC, HMC/EC, HPMC, titanium dioxide, and sucrose fatty acid ester mixture	[50,51]
9	Ibuprofen	Rotogranulation and coating	HEC, HPMC	[53]
10	Aspirin	–	Cellulose acetate latex and triacetin	[54]
11	Famotidine	Rotogranulation and coating	HPC, HPMC, cellulose acetate	[55]
12	Amoxycillin trihydrate	Granulation	MCC, L-HPC	[56]
13	Acetaminophen	Coating	Cellulose acetate, cellulose acetate butyrate, HPC/cellulose acetate, Eudragit E 100, PVP	[57,58]
14	Morphine HCl	Coating	Cellulose, Eudragit NE 30D	[59]
15	Amiprilose HCl	Coating	Calcium gluconate and sodium alginate	[64]
16	Terfenadine	Mixing	Sodium alginate, carrageenan, and macrogol-400	[65]
17	Beclamide	Microencapsulation	Gelatin	[68]
18	Clarithromycin	Rotogranulation	Carbopol, PVP	[70]
19	Roxithromycin	Granulation and coating	PEG, Eudragit L 100–55	[72]
20	Nizatidine	Spray drying	Eudragit E 100	[74]
21	Cetraxate HCl	Melt granulation and coating	Corn starch, Macrogol-6000, Eudragit S-100	[75,76]
22	Ciprofloxacin	Microencapsulation	Eudragit NE 30D, HPC	[78]
23	Ibuprofen	Spray coating	Eudragit L300, propylene glycol, mannitol, and flavor	[80]
24	Bifemelane HCl	Coating and spraying	Glycerin monostearate, Eudragit L30-D-55, PEG, sucrose	[81]
25	Cefuroxime axetil	Emulsion-solvent evaporation	Eudragit L-55 and RL	[110]
26	Pirenzepine and Oxybutynin	Dispersion coating	Eudragit E-100, MCC, HPC	[111]
27	Diclofenac	Microencapsulation	EC	[125]
28	Nicorandil	Coating	Crosscarmellose sodium, D-mannitol, and lactose	[132]
29	Levofloxacin	Coating	Eudragit E100, cellulose acetate	[141]

Note: HPMC, Hydroxypropyl methyl cellulose; HEC, Hydroxyethyl cellulose; HPC, Hydroxypropyl cellulose; L-HPC, Low substituted hydroxypropyl cellulose; CMC, Carboxy methyl cellulose; PVP, Polyvinyl pyrollidone; EC, Ethyl cellulose; MCC, Microcrystalline cellulose; PEG, Polyethylene glycol.

pH conditions. This suitably masks the unpleasant taste and odor of drugs.

Drug release from the resin depends on the properties of the resin and the ionic environment within the gastrointestinal tract (GIT). Drug molecules attached to the resin are released by exchanging with appropriately charged ions in the GIT, followed by diffusion of free drug molecule out of the resins.

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Ion exchange resins can be classified into four major groups:

- Strong acid cation-exchange resin.
- Weak acid cation-exchange resin.
- Strong base anion-exchange resin.
- Weak base anion-exchange resin.

Strong acid cation resins (sulfonated styrene-divinylbezene copolymer product) function throughout the entire pH range and can be used for masking the taste of basic drugs. Weak acid cation exchange resins function at pH values above 6.0. Similarly, strong base anion-exchange resins function throughout the entire pH range and can be used for masking the taste of acidic drugs, while the weak base anion exchange resins function well below pH 7.0.[64] Polystyrene matrix cation-exchange resins (Indion CRP-244, Indion CRP-254) have been reported to mask the bitter taste of chlorpheniramine maleate, diphenhydramine HCl, ephedrine HCl, noscapine HCl, and amphetamine sulphate.[87] Amberlite IRP-69, a cation-anion exchange resin, is used to mask the bitter taste of buflomedil.[88] Oral liquid products of quinolones (orbifloxacin) and/or their derivatives are formulated using ion exchange resins, such as methacrylic acid polymer crosslinked with divinylbenzene, as the carrier. The formation of a quinolone-resin complex (resinate) eliminates the extreme bitterness of the quinolones to make the liquid oral dosage form palatable. The preparation procedure involves dissolving the quinolone in an aqueous media followed by the addition of an ion exchange resin to form a drug/resin complex. The complex can be suspended directly into suitable vehicles with flavoring agents such as syrup base (malt extract) with the aid of an anticaking agent (colloidal silicone dioxide) and a preservative (sorbic acid).[89] To reduce the bitterness of erythromycin and clarithromycin, a polymer carrier system was developed by adsorption on Carbopol 934. Taste masking was further improved by encapsulating the adsorbate particles with polymer coatings. Hydroxypropyl methylcellulose (HPMC) phthalate (HP-55) provided the best combination of suspension stability, taste protection, and bioavailability.[90] Table 4 summarizes taste masking of drugs by complexing agents and ion-exchange resins.

MISCELLANEOUS TASTE-MASKING APPROACHES

By Effervescent Agent

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have also been employed for use as taste-masking agents for dosage forms that are not dissolved in water prior to administration. A chewing gum composition of bitter medicament(s) was formulated to supply the medicament(s) to the oral cavity for local application or for buccal absorption. It comprises a chewing gum base, an orally administrable medicament, a taste masking generator of carbon dioxide, and optionally a taste bud desensitizing composition (e.g., oral anesthetics such as benzocaine and spilanthol) and other nonactive materials, such as sweeteners, flavoring components, and fillers.[91] Recently, effervescent tablets of fentanyl and prochlorperazine were developed to supply these drugs to the oral cavity for buccal, sublingual, and gingival absorption. The formulations contain the drugs in combination with effervescent agent(s) to promote their absorption in the oral cavity and to mask their bitter taste. An additional pH adjusting substance was also included in fentanyl formulation for further promotion of absorption.[92]

Rheological Modifications

Increasing the viscosity with rheological modifiers such as gums or carbohydrates can lower the diffusion

Table 4. Drugs and taste masking complexing agents and ion exchange resins.

S. No.	Drug	Resin/complexing agent	Ref.
1	Carbetapentane citrate	Cyclodextrin	[84]
2	Ibuprofen	Hydroxypropyl β-cyclodextrin	[85]
3	Gymnema sylvestre	β-cyclodextrin	[86]
4	Chlorpheniramine maleate	Indion CRP 244, indion CRP 254	[87]
5	Diphenhydramine HCl	Indion CRP 244, indion CRP 254	[87]
6	Buflomedil	Amberlite IRP 69	[88]
7	Orbifloxacin	Amberlite IRP 69	[89]
8	Chloroquine phosphate	Indion 234	[122]

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of bitter substances from the saliva to the taste buds. Acetaminophen suspension can be formulated with xanthan gum (0.1–0.2%) and microcrystalline cellulose (0.6–1%) to reduce bitter taste.[93] The bitter taste of a syrup composition comprising of phenobarbital or acetaminophen was masked by using a polyhydric alcohol such as polyethylene glycol or polypropylene glycol with polyvinyl pyrollidone, gum arabic, or gelatin.[94] Gelatin and flavoring materials (chocolate flavor) mask the bitter taste of tannic acid by viscosity effects, when made into a jelly by cooling.[95] Also, an aqueous solution of tannic acid (0.1 g) and sodium alginate (0.4 g) had reduced bitterness compared to a solution of tannic acid alone in water.[96] The antidepressant drug mirtazapine is formulated as an aqueous suspension using methionine (stabilizer) and maltitol (thickening agent). Maltitol is stable in the acidic pH range of 2 to 3 and besides masking the unpleasant taste of the drug, it also inhibits its undesirable local anesthetic effect.[97] Other commercially available pharmaceutical compounds delivered using the present approach are pseudoephedrine HCl, dextromethorphan, and ibuprofen.[98]

Salt Preparation

Adding alkaline metal bicarbonate such as sodium bicarbonate masks the unpleasant taste of water-soluble ibuprofen salts in aqueous solution.[99] The bitter taste of caffeine may be masked by formulating it as a carbonated oral solid preparation using sodium bicarbonate, ascorbic acid, citric acid, and tartaric acid.[100] Magnesium aspirin tablets are rendered tasteless by preparing magnesium salts of aspirin.[64] Penicillin prepared as N,N′-dibenzylethylene-diamine diacetate salts or N,N′-bis (deyhdroabiety) ethylenediamine salts is tasteless.[64] Bitterness-reduced antitussive and expectorant compositions (tablets) of dihydrocodeine phosphate, DL-methylephedrine HCl, and D-chlorpheniramine maleate contain magnesium salts, sweeteners, starch, and cellulose.[101]

Solid Dispersion Systems

Solid dispersions can be defined as the dispersion of one or more active ingredients in an inert solid carrier. Solid dispersion of drug with the help of polymers, sugar, or other suitable agents, is very useful for taste masking. The bitter taste of dimenhydrinate can be masked by preparing the solid dispersion of the drug with polyvinyl acetate phthalate.[102]

Group Alteration and Prodrug Approach

The alkyloxyalkyl carbonates of the clarithromycin 2′ position have remarkably alleviated bitterness and improved bioavailability when administered orally.[103] Tasteless/bitterless prodrugs of opioid analgesics and antagonists were formulated for improved buccal delivery. Tasteless prodrugs of nalbuphine HCl, naltrexone, naloxone, oxymorphone HCl, butorphanonol, and levallorphan were synthesized for buccal administration to improve bioavailability relative to that of oral dosing without the characteristic bitter taste. In rats, the prodrugs demonstrated up to 90% bioavailability. It was concluded that when administered as prodrugs, bioavailability improved without visible adverse effects.[104]

Freeze Drying Process

This method is used to develop fast-dissolving oral technologies such as Zydis and Lyoc technology. Zydis is a tablet-shaped dosage form that spontaneously disintegrates in the mouth in seconds. This is due to the high porosity produced by the freeze drying process. The Zydis process requires the active ingredient to be dissolved or suspended in an aqueous solution of water-soluble structure formers. The resultant mixture is then poured into the preformed blister pockets of a laminate film and freeze dried. The two most commonly used structural excipients are gelatin and mannitol, although other suitable excipients can be used (e.g., starches, gums, etc.). This process is ideally suited to low-solubility drugs as these are more readily freeze dried. Taste is very important for this type of dosage form and it is possible to produce palatable formulations by using artificial sweeteners (e.g., aspartame) and conventional flavors. Lyoc differs from Zydis in that the product is frozen on freeze-dryer shelves.[105]

Various drugs have been taste-masked by Zydis technology. These are lorazepam (Wyeth), piroxicam (Pfizer), loperamide (Janssen), ondansetron (Glaxo Wellcome), rizatriptan (Merck), loratadine (Schering Plough), olanzapine (Eli Lilly), selegiline (Elan), scopolamine/chlorpheniramine (Taisho), etc.[105]

Wet Spherical Agglomeration (WSA) Technique and Continuous Multipurpose Melt (CMT) Technology

A novel microencapsulation process combined with the wet spherical agglomeration (WSA) technique was used to mask the bitter taste of enoxacin. The

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microcapsules prepared were bio-equivalent to the commercial Enoxacin 100 mg tablets in beagle dogs.[106] The CMT method was developed for the continuous granulation and coating of pharmacologically active substances. It was concluded that this method could be successfully applied for taste masking of bitter drugs.[107]

RECENT APPROACHES AND DEVELOPMENTS IN TASTE MASKING

Yajima[108] developed a method of taste masking using a spray-congealing technique to mask the bitter taste of clarithromycin. Glyceryl monostearate and aminoalkyl methacrylate copolymer E (AMCE) were selected as ingredients. The palatability and taste of optimized formulation (CAM: GM: AMCE, 3:6:1) were significantly improved, compared with conventionally coated granules. Later, Yajima, Umeki, and Itai[109] evaluated the effects of operating conditions in the spray-congealing process on taste masking release and the micro-meritic properties of clarithromycin wax matrix. Results showed that the congealing speed of melt droplets was the dominant factor in masking the bitter taste of drug.

Lorenzo-Lamosa et al.[110] prepared the microspheres of cefuroxime axetil using pH-sensitive acrylic polymers. Formulations made of Eudragit L-55 and RL in the ratios 100:0 and 90:10 were adequate in terms of the stability of the encapsulated Cefuroxime axetil. These polymer microspheres were shown to be efficient in masking the bitter taste of the drug.

Ishikawa et al.[111] prepared and evaluated tablets containing bitter tasting granules masked by the compression method. Pirenzepine HCl and Oxybutynin HCl were used as model drugs and Eudragit E-100, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate were used as excipients. The results showed that there was rapid in vitro release of Oxybutynin and Pirenzepine at pH 1.2. The tablets disintegrated within 20 seconds into the saliva of the volunteers and they did not report a bitter taste after disintegration.

Tozaki et al.[112] developed a multichannel taste sensor system to detect the suppression of bitterness by sweet substances. Quinine was used as a bitter drug and sucrose as a sweetener. The results showed that the suppression of the bitterness of quinine by sucrose could be quantified by using the multichannel system.

Lunstroth, Schill, and Siegrist[113] formulated a carboxymethyl cellulose gel with lemon flavor to improve the taste of gut layer solution. The gel was quickly mixed with the lavage solution and showed improved palatability.

Sugao et al.[114] performed taste masking of Indeloxazine HCl (IDX) powder without loss of bioavailability by heat treatment of wax-coated microparticles. Microparticles of IDX were coated with a mixture comprising hydrogenated oil and surfactants in a fluidized bed using the side-spray method. The dissolution rate was enhanced by heat treating the coated particles at a temperature above the melting point of surfactant in the coated layer. This method sufficiently suppressed the bitter taste of IDX powder without loss of bioavailability.

Barra, Lescure, and Doelker[115] proposed a new approach for taste masking of powders, which require neither the modification of existing formulation nor the use of costly technological operations. Different particle size fractions of two unpleasant tasting drugs (Niflumic acid and Ibuprofen) were blended in binary mixes with different particle size fractions of two flavorless excipients (ethyl cellulose and hydroxypropyl methylcellulose). By selecting the appropriate mixes of identical composition but different organizations, as predicted from surface energy data, it was possible to use the different organizations to modify the taste of the mixes.

Venkatesh and Palepu[116] formulated bite-dispersion tablets for masking the bitter taste of medicaments. These tablets disperse easily and quickly in the oral cavity after a gentle bite, without the aid of water. The process comprises preparing a dry granulation of one or more of the medicaments blended with suitable excipients, flavors, and a combination of a waxy material and phospholipid (BMI-60) or an intense sweetener derived from fruit flavonoids (neohesperidine) for taste masking. The blend is finally compressed into tablets.

Cano et al.[117] studied the stability and sensory effects of neohesperidin dehydrochalcone and its use in pharmaceutical formulation to mask the bitter taste.

Bakal and Snyder[118] developed various methods and compositions for masking the taste of minerals in ingestible products. In particular, tannic acid glycyrrhizin and acesulfame potassium are added to compositions comprising minerals such as potassium, calcium, magnesium, iron, copper, chromium, zinc, and mixtures in order to reduce or eliminate the unpleasant taste or aftertaste associated with these minerals.

Choi and Kim[119] developed a coated drug elixir system to mask the bitterness of Peonjahwan (an oriental traditional medicine that enhances the release

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of bilirubin). Coated peonja drug elixir (CPDE) was prepared by coating the peonja (crude active ingredient of Peonjahwan) with Eudragit acrylic resin. It was concluded that CPDE, which masked the bitterness of Peonjahwan and enhanced the release of bilirubin, is a preferred delivery system for Peonjahwan.

Salazar de Saavedra and Saavedra Cuadra[120] developed and applied a sensorial response model to determine the design and taste of the oral liquid pharmaceutical dosage form. Acetaminophen was used as the model drug. It was found that a mixture of sweeteners and an essence was the most efficient way of masking the bitter taste of acetaminophen.

Ishimaru et al.[121] examined a new diagnostic test using a bitterness masking substance, Benecoat BMI-60. It is a masking substance specific to the taste cells bitterness receptors. After patients gargled with BMI-60 solution, the phantom sensation of bitterness was masked in some patients but not in others. It was concluded that this test is useful for the diagnosis of phantom sensation of bitter taste.

Agarwal, Mittal, and Singh[122] formulated high-potency adsorbates of Chloroquine phosphate by batch method using a polyacrylic acid ion-exchange resin. Taste evaluation of the adsorbates showed significant masking of the bitterness of the drug. The complex formulation was complete at pH 6.0.

Friend et al.[123] developed a taste-masked microcapsule composition for oral administration of a drug. The composition comprised microcapsules of drug and a substantially water-insoluble polymeric material, typically a cellulosic polymer (ethyl cellulose). Taste masking was done by phase separation coacervation technique in which the drug was coated with relatively high levels of a polymeric material. These high coating levels gave rise to effective taste masking, while nevertheless allowing targeted release of drug, so that the drug was released shortly after passage through the mouth. Microcapsules were evaluated for flow, color, odor, mouthfeel/grittiness, taste masking, bitterness, aftertaste, and overall acceptance. The microcapsule composition may be incorporated into any number ofpharmaceutical formulations, including chewable tablets, effervescent tablets, powders, liquid dispersions, etc.

There is a continuing need to provide taste-masking agents for malflavored lip and oral cavity application products. Morefield and Tongaree[124] formulated a composition that removes or masks the taste of malflavored organic sunscreens with colloidal silicon dioxide. The composition is meant for topical application to the lips or oral cavity. The composition includes a topically applicable anhydrous base, a malflavored organic sunscreen, and colloidal silicon dioxide. The final composition also has a flavorent, a colorant, a nonorganic sunscreen, perfume, or any combination of the foregoing. The mixture had very little bitter aftertaste when applied to the lips.

Al-Omran et al.[125] studied the taste masking of Diclofenac Sodium (DS) using microencapsulation without interfering with an adequate rate of drug release. The DS microcapsules were successfully prepared using EC-toluene-petroleum ether. The prepared microcapsules were taste evaluated by a taste panel of 10 volunteers. The results showed that the palatability of DS was significantly improved by microencapsulation with sufficient rate of drug release from the microcapsules.

Li et al.[126] evaluated the effect of different grades of hydroxyethyl cellulose (HEC) and hydroxypropyl methylcellulose on film formulation and taste-masking ability using Ibuprofen as a model drug. Two grades of HEC combined with three grades of HPMC. All the results were satisfactory.

Duong et al.[127] developed a high-performance liquid chromatography (HPLC) assay method for coating integrity of topiramate sprinkle formulation. This method determines the completeness of the sprinkle coating and indirectly, the completeness of taste masking of the product. It is also used in formulation selection by screening sprinkle beads that contain different amounts of coating to see which formula can best mask the taste with an acceptable level of exposed topiramate drug substance. This method has been validated to meet Food and Drug Administration (FDA) validation guidelines.

Zheng et al.[128] evaluated the effect of taste-masking excipients (aspartame and menthol) on in vitro and in vivo performance of a Leuprolide metered-dose inhaler (MDI) suspension formulation. It was found that the longer milling time for the Leuprolide suspension with the taste-masking excipients was required to obtain a similar particle size distribution compared with the formula without taste-masking excipients using fluidized energy mill.

Hashimoto et al.[129] demonstrated the possibility of masking the taste of salts of basic drugs by microencapsulation with polyvinylacetal diethylaminoacetate (AEA) microspheres using a w/o/w emulsion solvent evaporation method. They formulated acid soluble, AEA microspheres containing trimebutine maleate using the above method and evaluated the taste-masking potential of this formulation in human volunteers. The results of a gustatory sensation test in healthy volunteers confirmed the taste-masking effects of the microspheres.

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Kidokoro et al.[130] investigated the effect of the crystallization behavior of Macrogol 6000 (polyethylene glycol 6000; PEG 6000), used as a binder, during the solidification process on the properties of mononucleic granules prepared by the fluidized hot-melt granulation (FHMG) technique. The results of this study suggested that the crystallization behavior of the binder during the solidification process of FHMG can influence the properties of the resultant granules, such as particle size distribution, taste masking, and content uniformity.

Saha and Hayashi[131] discussed the causes for the production of bitter peptides in various food protein hydrolyzates and the development of methods for the prevention, reduction, and elimination of bitterness as well as masking of bitter taste in enzymatic protein hydrolyzates. These methods include selective separation, such as treatment with activated carbon, extraction with alcohol, isoelectric precipitation, chromatography on silica gel, hydrophobic interaction chromatography, and masking of bitter taste. Bio-based methods include further hydrolysis of bitter peptides with enzymes such as aminopeptidase, alkaline/neutral protease and carboxypeptidase, condensation reactions of bitter peptides using protease, and use of *Lactobacillus* as a debittering starter adjunct.

Jin et al.[132] prepared and evaluated fast-disintegrating (FD) tablets of Nicorandil. A FD tablet containing nicorandil-loaded particles with 1%–4% crosscarmellose sodium in addition to D-mannitol and lactose (9:1) was prepared and examined. The results suggest that the formulation has a masking effect against the bitter taste and irritation of the drug.

Shimizu et al.[133] developed enteric-coated microgranules for the lansoprazole fast-disintegrating tablet (LFDT). These enteric-coated microgranules have the multiple functions of reducing the damage to the enteric layer during the compression process, improving the stability of lansoprazole, and masking the unpleasant bitter taste.

Pearnchob, Siepmann, and Bodmeier[134] investigated the potential of shellac to provide moisture-protective and taste-masking coatings as well as extended-release matrix tablets. The efficiency of shellac to achieve moisture protection and taste masking was compared with that of hydroxypropyl methylcellulose (HPMC). The stability of acetylsalicylic acid was higher in tablets coated with shellac compared with HPMC-coated systems, irrespective of the storage humidity. Therefore, lower shellac coating levels were required to achieve the same degree of drug protection. Shellac coatings also effectively mask the unpleasant taste of acetaminophen tablets. Lower coating levels were required to achieve similar effects as compared to HPMC.

Nakamura et al.[135] performed a study to quantify the degree of suppression of the perceived bitterness of quinine by various substances and to examine the mechanism of bitterness suppression. The following compounds were tested for their ability to suppress bitterness: sucrose, aspartame, sodium chloride (NaCl), phosphatidic acid (a commercial bitterness suppression agent), and tannic acid (a component of green tea). These substances were examined in a gustatory sensation test in human volunteers using an artificial taste sensor. Sucrose, aspartame, and NaCl were effective in suppressing bitterness, although at comparatively high concentrations. Similar levels of bitterness inhibition by phosphatidic acid and tannic acid (81.7%, 61.0%, respectively) were obtained at much lower concentrations (1.0% w/v for phosphatidic acid and 0.05% w/v for tannic acid). The mechanism of the bitterness-depressing effect of phosphatidic acid and tannic acid was investigated in terms of adsorption and masking at the receptor site. With phosphatidic acid, 36.1% of the bitterness-depressing effect was found to be due to adsorption, while 45.6% was due to suppression at the receptor site. In the case of tannic acid, the contribution of the adsorption effect was about 27.5%, while the residual masking effect at the receptor site was almost 33%. Further addition of tannic acid (0.15% w/v) increased the bitterness quinine, which probably represents an effect of the astringency of tannic acid itself. Finally, an artificial taste sensor was used to evaluate or predict the bitterness-depressing effect. It was concluded that the taste sensor is potentially useful for predicting the effectiveness of bitterness-depressant substances.

Suzuki et al.[136] developed various formulations with some matrix bases and corrigents for the development of oral acetaminophen chewable tablets with inhibited bitter taste. The tablets made of Witepsol H-15/Benecoat BMI-40/sucrose, Witepsol H-15/cocoa powder/sucrose, and Witepsol H-15/sucrose best masked the bitter taste as they were tolerable enough to chew and swallow. These dosage forms also showed good release of the drug, indicating little change in bioavailability due to masking.

Tanigake et al.[137] evaluated the ability of a taste sensor to determine the bitterness of clarithromycin powder suspensions of various concentrations and of a commercial clarithromycin dry syrup product (Clarith dry syrup, Taisho Pharmaceutical Co., Ltd., Tokyo, Japan) containing aminoalkyl methacrylate polymer as a taste masker. For Clarith dry syrup, the sensor output was small, suggesting that aminoalkyl methacrylate

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polymer was successful in almost complete masking of the bitter taste of the dry syrup product. The bitterness intensities of mixtures of 1 g of Clarith dry syrup with 25 mL of water, coffee, tea, green tea, cocoa, milk, and a sports drink were also examined. Coadministration of 1 g of Clarith dry syrup with an acidic sports drink was found to be the most bitter.

Itoh and Niwa[138] developed a rapidly releasing and taste-masking pharmaceutical dosage form (or pharmaceutical preparation) comprising a core containing a pharmaceutically active ingredient (Sildenafil citrate), low-substituted hydroxypropyl cellulose, microcrystalline cellulose, hydroxypropyl methyl cellulose, and calcium gluconate; an inner coating layer formed on the core and containing a water-soluble and water-insoluble polymer (hydroxypropyl methyl cellulose and Eudragit NE30D); and an outer coating layer formed on the inner coating layer and containing a saliva-insoluble polymer (Eudragit E 100). The outer coating layer mainly has a taste-masking effect to prevent an active ingredient from being released when a patient holds a coated drug in the mouth. The dosage form may further comprise a sugar coating layer formed on the outer coating layer. Results confirmed that the oral dosage forms of this invention have good taste-masking properties and good drug release profiles.

Meneaud, Al-ghazawi, and Elder[139] developed a water dispersible formulation of Paroxetine for immediate oral administration. It comprises a dry blend of paroxetine, a water soluble dispersing agent (polyvinyl pyrollidone/calcium carbonate/sodium starch glycolate), and a taste-masking agent (Eudragit L30D55/β-cyclodextrin/lecithin/Polacrilin K) as a dispersible powder along with flavors and sweeteners.

Carbo et al.[140] developed a coating composition that masks the undesirable taste of a pharmaceutically active ingredient that is consumed orally. The coating composition has polyvinyl acetate, and a dimethylaminoethyl methacrylate and neutral methacrylic acid ester (Eudragit E100). Optionally, an alkaline modifier, such as triethanol amine may be included in the coating composition to enhance release of the active ingredient.

Yu and Roche[141] formulated taste-masked pharmaceutical liquid formulations of Levofloxacin for oral administration. The liquid composition utilizes a ''reverse enteric coating,'' which is soluble in the acidic pH of the stomach, generally about 1–4, but relatively insoluble at the nonacidic pH of the mouth. The coatings encapsulate the active ingredient and thereby effectively mask its taste and also provide for rapid release and absorption of the drug, which is generally desirable in the case of liquid dosage forms. The optimized core composition consists of Levofloxacin (9.836), Eudragit E100 (4.328), and cellulose acetate (6.492) in acetone (79.344). Acetone is removed during the process and does not appear in the final product. Following coating of the Levofloxacin particles, the coated particles are admixed with the adjuvants (sodium bicarbonate, microcrystalline cellulose, carboxy methyl cellulose, sucrose, and flavors) to form a liquid composition for oral administration suitable for pediatric use.

Dobetti[142] developed a formulation for preparing a fast-disintegrating tablet comprising a drug in multiparticulate form, one or more water-insoluble inorganic excipients, one or more disintegrants, and optionally one or more substantially water-soluble excipients. The amounts of said ingredients were such as to provide a disintegration time for the tablet on the order of 75 seconds or less, typically 30 seconds or less. Ibuprofen was used as the model drug. These tablets are particularly suitable for rapidly releasing a water-soluble or water-insoluble drug in granular or microencapsular form, e.g., where the drug is for controlled, sustained, or targeted release, or where the drug requires gastric protection or taste masking, etc. Coated microparticles having taste-masking properties are obtained by phase separation (coacervation), since this process ensures the most uniform coverage of a drug substance. The drug microcapsules, along with normal tablet excipients (crosscarmellose sodium, microcrystalline cellulose, crosspovidone, dibasic calcium phosphate, silicon dioxide, lactose magnesium stearate, talc, etc.), sweeteners (saccharin/aspartame), and flavors (banana/strawberry/mint), are finally compressed into tablets.

Nouri et al.[143] developed a method for manufacturing coated granules with masked taste and instant release of the active principle. Coated granules of Eletriptan, Ibuprofen, and Pregabaline were prepared using a coating polymer (ethyl cellulose), a granule disintegrant (sodium crosscarmellose/crosspovidone), a membrane disintegrant (sodium crosscarmellose/crosspovidone), a permeabilizer (polyoxyethylene glycol 6000/hypermellose), a sweetener (aspartame/potassium acesulfam), and an antistatic agent (precipitated silica). The resulting coated granules were dried and incorporated into a fast-crumbling multiparticulate-type tablet. The tasting tests performed on the tablets were satisfactory and taste of active principle was not detected in any of the formulations.

Zyck et al.[144] developed antacid coated chewing gum products coated with high viscosity materials. The chewing gum composition consists of a water-insoluble chewable gum base portion (comprised of elastomers, resins, fats and oils, softeners, and inorganic fillers), a

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water-soluble bulk portion (comprised of bulk sweeteners, high-intensity sweeteners, flavoring agents, softeners, emulsifiers, colors, etc.), and typically water-insoluble flavoring agents (citrus oils, fruit essences, peppermint oil, spearmint oil, etc.). The water-soluble portion dissipates with a portion of the flavoring agent over a period of time during chewing. The coating on the cores produces a high viscosity in saliva when the gum is chewed. The gum base portion is retained in the mouth throughout the chew. For coated antacid chewing gum type products, the high level of calcium carbonate or other antacid in the coating modifies the taste quality and gum texture. The addition of high-intensity sweeteners to the gum coating improves the taste of the finished product.

CONCLUSION

Taste masking of bitter drugs has significantly improved the quality of treatment provided to suffering patients, especially children. There are so many effective techniques and methodologies that are constantly being researched and developed in the pharmaceutical field in response to the need of taste masking. Applicability of all these approaches varies from drug to drug and depends on the type of dosage form required. The ideal solution to bitterness reduction or inhibition is the discovery of a universal inhibitor of all bitter-tasting substances that does not affect the other taste modalities such as sweetness. But to date there is no single substance that acts as the universal inhibitor of a bitter taste. Research for the same has been performed for a long time. Lipoproteins composed of phosphatidic acids and beta-lactoglobulin[37] and freeze-drying technology to prepare dissolving tablets[105] have great potential for taste masking. Lipoproteins selectively and reversibly inhibit the response to bitter taste, but more importantly do not suppress sweet, sour, or salty taste. They are at the leading edge of substance-universal bitterness inhibition. Other lipids such as triglycerides, diglycerides, and phosphatidylcholine with beta-lactoglobulin did not show any marked effect. New research on a bitterness inhibitor should focus on substances of a natural origin to permit their commercial use in improving the palatability of oral pharmaceuticals. It is also suggested that the multichannel taste sensor for the detection of suppression of bitterness by sweet substances[112] and other sensory evaluations of oral dosage forms of bitter drugs with taste inhibitors need to be further investigated for future applications. This would help in the development of more palatable and acceptable dosage forms.

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