REVIEW

Strategies for beating the bitter taste of pharmaceutical formulations towards better therapeutic outcomes

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Oral drug delivery remains the most favored method of administration due to its convenience and patient compliance. However, the unpleasant taste of certain medications often leads to poor acceptance, particularly among pediatric and geriatric patients. To address this issue, taste-masking (TM) technologies have emerged as effective solutions for improving the palatability of oral drugs. This review provides an overview of the key features of TM technologies, including the properties of materials used, their mechanisms, and applications in drug delivery. Typically, TM materials work by complexing or encapsulating drug molecules to prevent direct interaction with taste receptors, thus mitigating unpleasant flavors and enhancing the overall sensory experience. The review explores a range of materials—both synthetic and natural—and various TM technologies designed to mask bitter taste. Additionally, it discusses the latest methods for assessing the effectiveness of TM and the current regulatory landscape surrounding the use of these technologies in drug delivery.

1. Introduction

Taste can have several meanings depending on the context, but its primary definition relates to the sense of taste, which is one of the five basic human senses, along with sight, touch, hearing and smell. In this context, "taste" refers to the ability to perceive taste and distinguish between different flavours in food and beverages. It involves the sensory experience of sweet, sour, bitter, salty, and umami (savoury) flavours.[1]

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Specialised taste cells that are grouped together in tiny clusters are called taste buds, which are mostly found on the soft palate and dorsal surface of the tongue and help to detect stimuli.[2] These cells are activated by chemical signals, specifically neurotransmitters, which trigger the transmission of taste information to the brain. The brain processes this taste information to create the perception of flavour and generate an appropriate response.[3] Chewable tablets, liquids, and suspensions are the most common oral paediatric drugs in the market today. Additionally, orally dissolving films, mini-tablets, and orodispersing/disintegrating tablets are becoming more popular.[4] Healthcare professionals face a major problem when it comes to oral delivery of bitter drugs that are prescribed for paediatric patients. A good oral dosage form should have inbuilt bitterness inhibition and reduction ingredients or mechanisms as important aspects to improve patient compliance. The palatability of these formulations has improved through proven techniques for bitterness inhibition and reduction. If reduced bitterness can be achieved to some extent, the creation of oral formulations as alternatives for typically injectable formulations may become more prevalent. If reduced bitterness can be achieved in oral formulations, it could significantly impact the pharmaceutical industry by making oral medications a more viable alternative to injectable formulations. Traditionally, injectables are preferred for drugs with unpleasant tastes or those that require rapid absorption and high bioavailability. However, with advancements in formulation technology that mitigate bitterness, pharmaceutical companies might be encouraged to develop more oral drugs instead of injectables. This shift could be driven by several factors. For one, oral formulations are generally more convenient and less invasive, which could improve patient compliance and reduce healthcare costs associated with injections. In recent years, there has been significant progress in developing compositions that are bitterless, tasteless, or taste-masked. To mask the bitter taste of drug substances, three different approaches are undertaken in general, namely, (a) physical barriers, (b) change taste perception, and (c) change drug solubility.[5] To explain more specifically, taste masking can be achieved by the addition of flavouring agents,[6] sweeteners and amino acids,[7] polymer coating,[8] conventional granulation,[9] ion-exchange resins,[10] spray congealing with lipids,[11] inclusion complex formation with cyclodextrins,[12] freeze-drying,[13] multiple emulsification,[14] and also taste masking by gelatin or liposome encapsulation.[15] More recently, research has been done with excipients that block the bitter taste receptor and prevent taste perception.[16] Thus, any pharmaceutical formulation with a tasty flavour is certainly preferable over a competitor's product, resulting in higher patient compliance and therapeutic benefits as well as increased sales and profits for the company. Numerous formulations with enhanced efficacy and acceptance have been created due to a desire to make these products more palatable. Masking undesirable APIs is desirable if they are included in solid oral formulations, intended to release the API within the oral cavity, for example, orodispersible tablets (ODTs), which in most cases release the medicament in the oral cavity. However, patient compliance may be affected by the bitter taste of many active components; that is why the pharmaceutical industry is investigating new taste-masking technologies to improve the palatability of ODTs. ODTs have been linked to high patient compliance rates, particularly in the case of paediatric, geriatric, and mental patients who lack access to water or who have trouble swallowing conventional tablets.

Taste masked formulations are predominantly developed for paediatric and geriatric populations. Both children and elderly patients often face significant challenges with medication compliance due to the bitter taste of drugs. The unpleasant taste of many therapeutics is a notable barrier, particularly for children, who are highly sensitive to bitter flavours and may strongly refuse to take such medications. Additionally, elderly patients may experience altered taste sensitivity or have difficulty swallowing, further complicating medication adherence. Consequently, taste masking is a critical factor in ensuring patient compliance with therapeutic regimens. Developing novel taste masking technologies is essential to prevent children from experiencing unpleasant tastes and to enhance compliance among paediatric and geriatric patients.

Exact statistics on bitter medicines for children are not readily available, but it is well known that many medications, especially those for serious conditions, have a bitter taste, which can hinder medication adherence in children. In the USA, 1 in 12 children are on psychiatric drugs, many of which are bitter. In Australia, the rates of children on mental health-related medications are 0.2% for those under 5, 4.3% for ages 5–11, and 8.2% for ages 12–17 years. Common bitter compounds include chloroquine (5%), quinine (10%) for malaria, and caffeine (8%) in respiratory medications. Erythromycin (15%) and certain antibiotics like metronidazole (17%) are also noted for their bitterness. Acetaminophen (25%), a widely used pain reliever and fever reducer, and dextromethorphan (20%), a common cough suppressant, are particularly unpleasant in taste. These bitter molecules can significantly affect children's willingness to take their medications, highlighting the need for strategies to mask the bitterness.[17]

The main objective of this review is to explore the taste masking technologies of bitter drugs in accordance with drug delivery, target use of proper taste masking polymers, taste masking agents, and flavours which are easily compatible with active drugs. This article also reviews various techniques for taste-masked formulation development, strategies for taste masking, instrumental techniques for the measurement of the extent of taste masking, the current regulatory perspective, and the future perspective of taste-masked formulations.

2. Mechanism of taste sensations

Specific ion channels and second messenger systems are needed for the conversion of taste signals from chemical stimuli to electrical impulses for transmission to the brain.

The specific type of transduction system used depends on the taste itself.[18] As was previously noted, apical ion channels detect salty and sour tastes, while G protein-coupled receptors (GPCRs) detect bitter, sweet, and umami tastes. Various taste sensations in the tongue are shown in Fig. 1, and their mechanism of sensation is shown in Fig. 2.

2.1. Salty and sour tastes

The taste pores and their gustatory hairs come into contact with the Na^+ and H^+ ions present in salty and sour molecules, respectively. An intracellular cascade is started when the ions attach to their unique receptors on a taste receptor cell (TRC) inside the taste bud.[19] Voltage-gated channels become active as the cell membrane depolarizes. A cell's extracellular calcium influx causes the release of neurotransmitters into the synaptic cleft, which are then transported to the brain *via* the corresponding cranial nerve.[20]

2.2. Sweet, bitter, and umami tastes

A GPCR is bound by sugar, alkaloids, or L-amino acids, which activates a common signalling pathway. These GPCRs trigger the phospholipase C (PLC) pathway once they are turned on. Through the activation of inositol triphosphate (IP3) receptors, calcium is released from endoplasmic reticulum storage. With sodium inflow, this calcium release induces membrane depolarisation and the release of neurotransmitters. The connected cranial nerve then transmits taste information to the brain.[20]

The nucleus tractus solitorius (NTS) of the medulla receives signals from the vagus nerve, the glossopharyngeal nerve, and the chorda tympani branch of the facial nerve. From here, information travels to the postcentral gyrus, where it is sub-

merged by the lateral sulcus, and then to the ventral postero-medial nucleus (VPM) of the thalamus. Gustatory information is also received by the lateral hypothalamus and the central nucleus of the amygdala, which are also involved in the emotional aspect of taste, such as the memory of taste, and contribute to ingestive behaviour.[22]

Taste buds have their own taste coding. Sweet, bitter, umami, sour, and salt cells are specific taste cells that are responsible for sensing each taste quality. Sweet, bitter, and umami taste cells are grouped together as type II cells because they share the same signalling cascade, but sour taste cells are classified as type III cells. It should be noted that bitter and sour flavours play a key role in enhancing the perception of high salt taste. Traditional vesicular synapses are used for neurotransmission during sour transduction in type III cells, which also involves OTOP1 and Kir2.1 as the H^+ sensor and signal amplifier channels, respectively. Although sweet, umami, and bitter type II cells have different types of taste receptors, they all follow the same signalling route in which the activation of TRPM5 channels results in depolarization that causes action potentials to fire. Na^+ inflow through ENaC triggers sodium taste transduction by causing supra-threshold depolarization that leads to the production of action potentials. The channel synapse containing CALHM1/3 channels is used by both type II cells and sodium taste cells as the route for action potential-dependent neurotransmitter release. Here, Kir2.1 represents the inward rectifier K^+ channel, OTOP1 refers to otopetrin1, phospholipase C2 is represented by PLC2, inositol trisphosphate is abbreviated as IP3, diacylglycerol is expressed as DAG, ER represents endoplasmic reticulum, transient receptor potential melastatin is abbreviated as TRPM, calcium homeostasis modulator is represented as CALHM, and epithelial Na^+ channel is represented as ENaC.[21]

3. Strategies for taste masking

Taste masking is crucial in various industries like pharmaceutical, food and cosmetics to make products more palatable. In the pharmaceutical sector, taste masking is one of the prime important criteria, as for few medicines, bitter taste can influence the treatment outcome also. Particularly in the case of protease inhibitors, the bitter taste can highly impact the therapeutic outcome for acquired immunodeficiency syndrome (AIDS)-affected children. Here in this review, we tried to focus on various taste masking strategies like coating, sweeteners, granulation, microencapsulation, solid dispersion, complexation, pH modifiers, rheological modification and fast dissolving approaches towards developing well-tolerable medications for kids, which can simultaneously improve patient compliance and meet the highest possible therapeutic goals (Fig. 3).

3.1. Taste masking by coating

The most common technique for masking bitter or unpleasant drugs is polymer coating or physical barriers. Active pharmaceutical ingredients coated with a physical barrier successfully
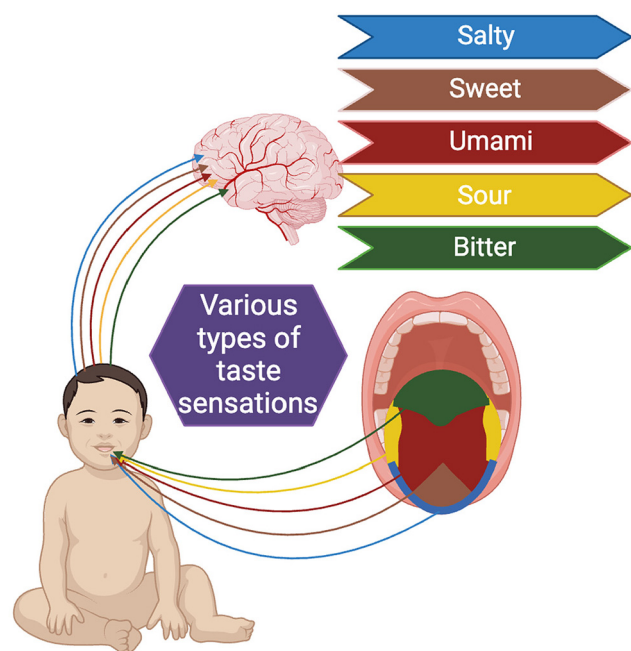

Fig. 1 Schematic representation of the five basic taste sensations on the human tongue.
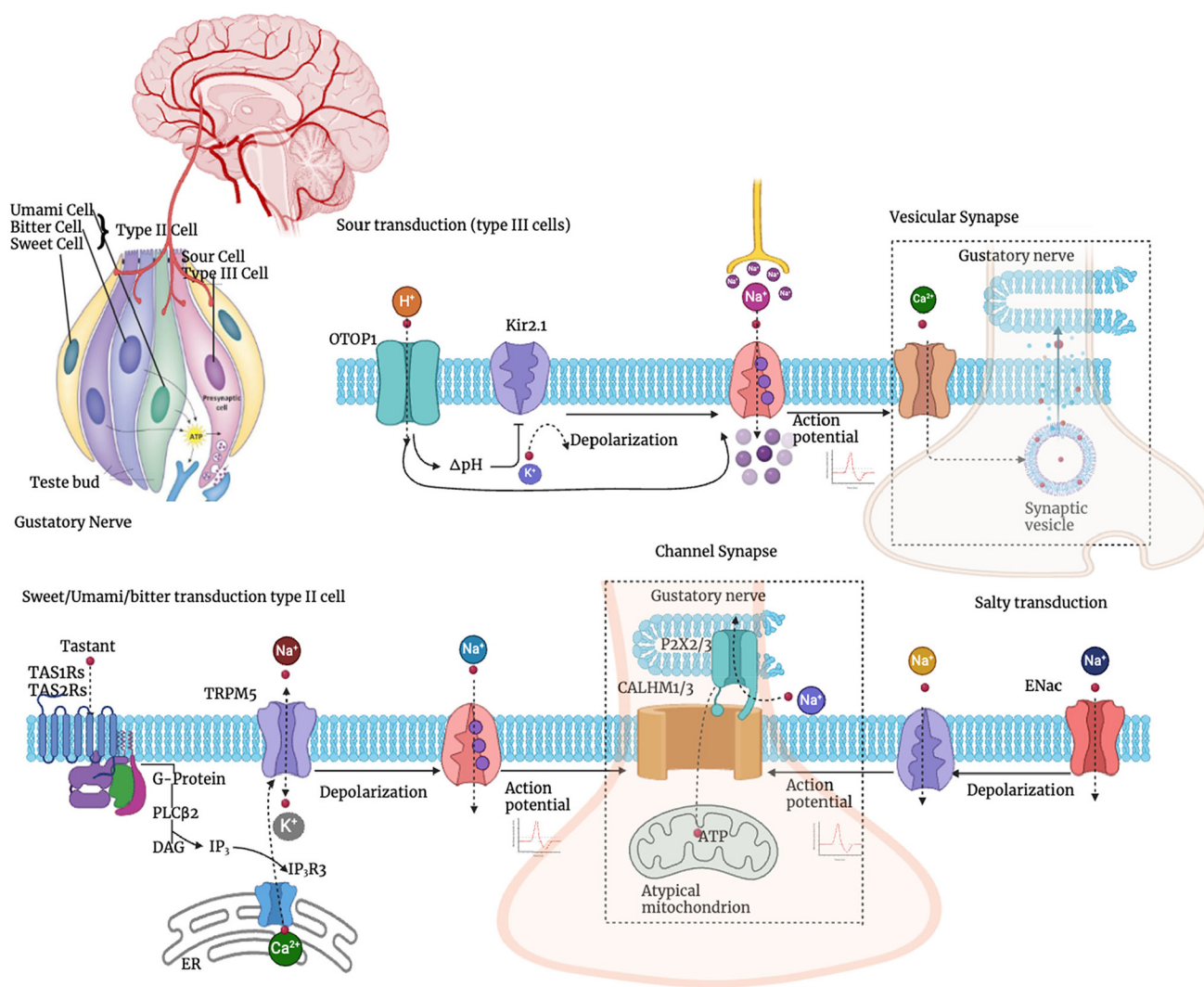
Fig. 2 Signal transduction and taste sensation mechanisms by the human brain.[21]

give palatable oral formulations, and quick dissolution of the API (drug) can be prevented in the mouth by coating. When the tablet disintegrates, the large, insoluble coated drug particles may remain in the mouth, creating a gritty and sandy feeling in the mouth cavity. This also brings up concerns with traditional tablet formulations since any reduction in palatability is something we want to avoid. Fluidised bed coating is a common approach for coating a core particle in a continuous layer. When using the fluidised bed coating approach, there are typically two types of procedures that can be used—coating with a molten mass or using a polymeric solution. The conventional coating method is commonly used for taste masking. It does need an evaporating solvent from solutions or dispersions to coat the material of interest. This approach offers a wide variety of acceptable polymers that are suitable for masking the taste of bitter drugs or preventing the grittiness of the coated particles. Depending on the granule characteristics of the active ingredients, the polymer content varies from 10 to 40% w/w. A few bitter drug substances which are

processed for formulation development using taste masking technology by polymer coating are presented in Table 2. The coating process is categorized based on the solvent system employed, the coating material utilized, and the number of coating layers applied. Hydrophilic polymers, hydrophobic polymers, sweeteners, and lipids are used alone or in combination as coating materials for masking the bitter taste.[16]

Encasing the bitter-taste drug particles inside a polymer coat lessens the bitterness perception by preventing the drug from dissolving in saliva. Nevertheless, there are drawbacks to this technique as well. These include the potential complexity and expense of the coating process, the requirement for exact control over coating parameters to guarantee uniformity and efficacy, and the potential to alter the drug release profile, which may have an impact on the therapeutic efficacy of the drug and performance of the dosage form.

3.1.1 Types of materials used for taste masking by coating. Polymer-based taste masking is a common approach used in pharmaceuticals to mask unpleasant taste. For taste masking
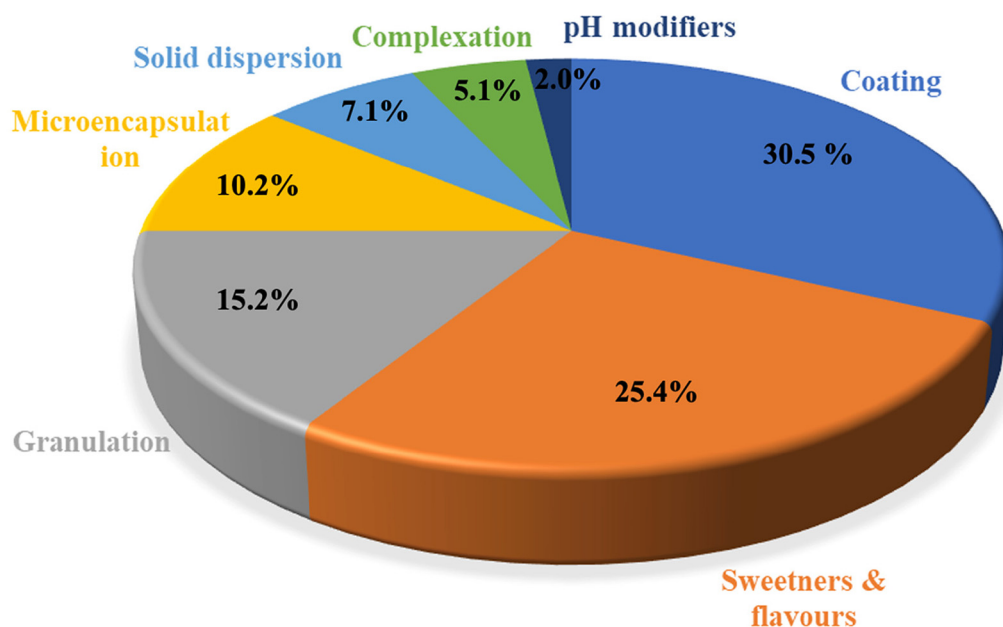
Fig. 3 Currently used taste masking strategies for the development of better formulations.

purpose, various types of polymers are used, namely, natural, semisynthetic and synthetic.

3.1.2 Natural polymers. The selection of polymers for taste masking of bitter drugs depends on the dosage form, specific drug and formulation requirements. By improving the palatability of drugs while maintaining their therapeutic efficacy, they contribute to enhancing patient compliance and acceptability. Various natural polymers can be included in pharmaceutical formulations to change the bitter taste of different drugs. Natural sources of polysaccharides include algae (alginates), animals (chitosan and chondroitin), plants (pectin, guar gum and mannan) and microbes (dextran and xanthan gum). Many advantageous characteristics of monosaccharide polymers include their high stability, hydrophilicity, lack of toxicity, ability to form gels, biodegradability, and having flexibility for chemical modification by simple techniques.

Various natural substances are employed in the pharmaceutical dosage form to mask the taste of bitter drugs. Gelatin, derived from collagen, forms a tasteless coating around tablets and capsules. Acacia gum, sourced from the acacia tree, provides a glossy coating that can regulate drug release. Alginates, extracted from brown seaweed, are added to liquid formulations for taste masking. Starches like potato, cornstarch, and tapioca are utilized for chewable pills' coatings.[23] Pectin, found in fruits, enhances the taste of chewable tablets or gummies.[24] Chitosan, derived from crab shells, aids in both taste masking and drug release enhancement.[25] Guar gum, obtained from the guar bean, serves as a binder and taste-masking agent in tablets and granules.[26] Agar, derived from seaweed, is used to mask the taste of drugs in oral formulations.[27] Xanthan gum, produced

by fermenting carbohydrates, acts as a suspending agent and taste-masking agent in liquid formulations.[28] Gellan gum, obtained from bacteria, facilitates controlled drug release while masking bitter taste.[29,30]

3.1.3 Synthetic and semisynthetic polymers. Polymer selection is crucial for effective taste masking through coating. The performance of the finished dosage form is significantly affected by the physicochemical and biological properties of the polymer, such as its ability to form films, lack of toxicity, and biodegradability.[31,32] There are various kinds of synthetic and semisynthetic polymers available, which are frequently used in taste masking, and are majorly categorized as water-soluble and insoluble. By mixing the water-insoluble and water-soluble polymers in a variable ratio, a taste-masking layer can be formed. Water-soluble polymers dissolve, disperse, and swell in water, altering the physical properties of aqueous systems by gelation and thickening. Traditionally, synthetic vinyl polymers and cellulose ethers (methylcellulose and HPMC) are used as water-soluble polymers for masking taste. Polymers and their mixtures that are insoluble at neutral pH are the most effective taste-masking agents. Ethyl cellulose and methacrylic copolymers are frequently used in taste masking. They act as an effective barrier against the transfer of drug molecules to the surface and water molecules to the core because they are insoluble at the neutral pH of saliva.[33,34] This produces a taste-masking effect. However, for water-insoluble polymers, organic solvent is not recommended for taste masking. Therefore, various polymers from this class are synthesised in the latex or pseudo-latex form in order to minimise the usage of organic solvents during the coating process.

Table 1 List of synthetic polymers used for taste masking of pharmaceutical products

Polymer types	Polymer	Molecule of interest	Ref.
Polymethacrylate	Eudragit EPO	Acetaminophen	38
		Chlorpheniramine maleate	39
		Donepezil HCl	40
		Ibuprofen	41
		Itopride HCl, prednisone	42
		Metoclopramide HCl	43
		Ondansetron HCl	44
		Quinine sulphate	45
		Sumatriptan succinate	46
		Trimetazidine HCl	47
	Eudragit E100	Clarithromycin	48
		Ornidazole	49
		Ondansetron HCl	50
		Ofloxacin	51
		Indinavir	52
		Sildenafil citrate	53
		Naproxen	54
		Pirenzepine and oxybutynin HCl	55
Polymethacrylates	Eudragit L30D-55	Ibuprofen and roxithromycin	56
	Eudragit L100-55	Cefuroxime axetil	57
		Cetirizine HCl	58
		Verapamil HCl	58
	Eudragit L30 D	Clarithromycin and erythromycin	59
	Eudragit S100	Roxithromycin	60
Polymethacrylates	Eudragit RL	Cefuroxime axetil	57
	Eudragit RS	Enoxacin	61
	Eudragit RL 30D	Cetirizine HCl	62
	Kollicoat Smartseal 30 D	Ornidazole	61
Polyacrylic acid	Carbopol 934	Erythromycin and clarithromycin	63
	Carbopol 934P	Dihydroartemisinin	64
	Carbopol 971	Enrofloxacin	65
Polyvinyl pyrollidone (PVP)	PVP K90 + PVAP	Ibuprofen	66
	Kollidon VA 64	Acetaminophen	67
Polyvinylacetal diethylaminoacetate	AEA	Trimebutine maleate	68

Table 2 Most commonly used coating polymers for taste masking of pharmaceuticals

APIs/drugs	Materials used	Technique	Ref.
Acetaminophen	Cellulose acetate butyrate, cellulose acetate, HPC/cellulose acetate, Eudragit EPO	Film coating	71
Amiprilose HCl	Sodium alginate and calcium gluconate	Spray coating	72
Levofloxacin	Cellulose acetate, Eudragit E100	Enteric coating	73
Nicorandil	D-Mannitol, lactose and croscarmellose sodium	Granulation and coating	74
Diclofenac	Ethyl cellulose	Granular coating	75
Oxybutynin and pirenzepine	HPC, MCC, Eudragit E100	Dispersion coating.	76
Bifemelane HCl	Sucrose, PEG, glycerin monostearate, Eudragit L-30-D-55	Coating and spraying	7
Cetraxate HCl	Eudragit S-100, Macrogol-6000, corn starch	Melt granulation and coating	7
Ibuprofen	Mannitol, propylene glycol, Eudragit L300 and flavour	Spray coating	41
Tramadol hydrochloride	Eudragit E 100	Mass extraction technique	77
Terfenadine	Carrageenan, sodium alginate, macrogol-400	Mixing	7
Morphine HCl	Eudragit NE 30D	Pellet coating	78
Famotidine	HPMC, HPC, cellulose acetate	Rotogranulation and coating	79
Enoxacin	HPMC, EC, HPC, Eudragit RS	Granulation and coating	80
Sparfloxacin	HPMC, HMC/EC, EC, titanium dioxide, L-HPC and sucrose fatty acid ester mixture	Granulation and coating	7
Cefeanel daloxate HCl	EC, HPMC, PVP, trisodium citrate	Granulation and coating	7
Triprolidine HCl	HPMC	Dispersion coating	81
Ibuprofen	Methacrylic acid copolymer (Eudragit)	Air-suspension coating	82
Propantheline bromide	EC, L-HPC	Granulation and coating	7
Pinaverium	Shellac or cellulose	Film coating	7
Aspirin	Triacetin and cellulose acetate latex	Rotogranulation and coating	83

Copolymers of acrylate and methacrylate and copolymers of ethyl acrylate, ethyl cellulose and methyl acrylate occur in the dispersion of the latex or pseudo-latex form.[35] Various polymer mixtures like Eudragit® EPO ReadyMix, Aquacoat® ECD, Sepifilm® TMLP, Kollicoat SmartSeal® 30 D and Opadry® AMB are utilized for taste masking of pharmaceuticals.

Examples of major water soluble polymers are methyl-cellulose – MC (Methocel® and Metolose® SM-4) and hypro-mellose – HPMC (Pharmacoat®, Sepifilm® LP, Spectracel® and AnyCoat® C); the derivatives of cellulose are included in this group. Cellulose naturally appears as a white, odourless, crystalline powder. Alpha-cellulose, derived as a pulp from fibrous plant sources, is hydrolysed with diluted mineral acid solutions to form it. Different types of cellulose are commercially available in different particle sizes and with different moisture and viscosity levels. Various cellulose ethers can be used in a variety of products.[36,37] Some cellulose ethers that are water soluble are methylcellulose (MC), sodium carboxymethyl cellulose (Na-CMC), hydroxypropyl methylcellulose (HPMC), and hydroxyethyl cellulose (HEC). For odour and taste masking applications, MC and HPMC are widely used. Some HPMC-containing film coating products that are commercially available are Spectracel®, Pharmacoat®, AnyCoat® C, and Sepifilm®. The viscosity of the polymer dispersion used improves the effectiveness of taste masking. A list of the most explored synthetic polymers used for the masking of bitter taste is given in Table 1.

A water-insoluble polymer cellulose ether, i.e., ethyl cellulose (EC) (Aquacoat®, Ethocel® and Surelease®), was synthesized by the reaction of alkali cellulose with ethyl cellulose. There are mainly aqueous and organic dispersions of ethyl cellulose. EC is a powder or granular material which is white to light tan in colour and has a melting point between 240 and 255 °C. It is mostly utilised in oral formulations and is stable against light, oxygen, heat and chemicals. The extent of drug release is varied with the molecular weight of ethyl cellulose. Ethyl cellulose is widely utilised in the microencapsulation process as a modified release polymer in addition to exhibiting taste masking capability. Ethocel® is a commercially available product of ethyl cellulose. It dissolves in a variety of solvents, including natural oils, aliphatic alcohols, and chlorinated solvents. It is practically insoluble in propylene glycol, glycerine and water.[69] Eudragit® E PO, Eudragit® E 12.5, Eudragit® E PO ReadyMix, Eudragit® E 100 and Kollicoat SmartSeal® 30 D are the copolymers based on acrylic and methacrylic acids. They are produced by polymerising methacrylic and acrylic acids or their esters. Through the formation of salts, poly(meth)acrylates become soluble in digestive fluids; pH-dependent release of the active component is made feasible by the acidic or alkaline groups in Eudragit® L, S, and E polymers.

They are used to control drug solubilization by covering or concealing the drug in direct contact with the fluids present in the mouth cavity by exhibiting taste-masking properties. Eudragits are categorised into cationic, anionic and neutral polymers. To mask a bitter taste and keep moisture out, manufacturers frequently use the cationic Eudragit series E.[70]

3.2. Taste masking by sweeteners, flavours and amino acids

A straightforward approach for taste masking in formulations like oral liquids, chewable tablets or other paediatric formulations is generally achieved by addition of sweeteners, flavours and amino acids. However, for highly water soluble and highly bitter drugs, this technique is not successful. To increase the efficiency of these techniques, flavours and artificial sweeteners are used with other taste masking techniques. Selection of flavour is very crucial for achieving the desirable extent of taste masking in highly bitter drugs. The details of flavouring agents containing paediatric formulations are given in Table 3. Many drugs administered to the oral cavity, such as mouthwashes and dentifrices, often lead to an unpleasant taste. To counteract this, the addition of isoborneol, borneol, or fenchone can effectively mask the undesirable flavours of certain formulations. This is particularly useful for cough drops and mouthwashes that contain medicinal, bitter-tasting ingredients like eucalyptus oil. Some flavouring agents have a cooling effect that helps individual feel less bitter. Primarily, numbness in the taste buds quickly gives a cooling effect after administration. Although the product's temperature has not changed physically, the brain still perceives it as cool. Janovasky and Wesley proposed a list of recommended flavours for masking a particular taste sensation.[84]

It is common practice to use sweeteners, flavours, and amino acids to mask the taste of supplements and medications to make them more palatable. Sweeteners such as sucralose and aspartame can effectively mask bitter taste, increasing the product's acceptability, particularly for younger consumers. However, their use raises questions about potential allergic reactions and long-term health effects. Although flavours like fruit or mint have a pleasant and adaptable masking effect, they can also be overpowering or not to everyone's taste. Amino acids, such as leucine and glycine, can lessen the bitterness and increase the umami flavour, providing a natural substitute with extra nutritional advantages; however, they may change the pH of the product or interact

Table 3 A few marketed formulations with specific flavouring agents

Dosage form	Dosage form	Flavouring agent	Ref.
Cefuroxime axetil	Granules for oral suspension	Tutti frutti flavour	85
Raltegravir	Granules for oral suspension	Banana with natural flavour	86
Azithromycin	Microsphere for oral suspension	Artificial cherry flavour	87
Abacavir sulfate	Oral solution	Artificial strawberry and banana flavour	87
Dolasetron mesylate	Injection solution (for oral dosing)	Apple or apple grape juice	87
Amprenavir	Oral solution	Artificial grape bubblegum flavour	87
Fluoxetin HCl	Oral solution	Mint	87
Ritonavir	Oral solution	Creamy caramel flavour	87

with the active ingredients. Achieving efficient taste masking without sacrificing the product's stability, efficacy, or safety still has numerous unattended gaps which require extensive research.

3.2.1 Types of flavours. Flavours are divided into two main categories: natural and synthetic. Natural flavours encompass a variety of sources, including spirits like lemon and orange extracts, raspberry juices, blackcurrant syrups, and aromatic elements like anise and cinnamon waters. Extracts such as liquorice, tinctures like ginger, and aromatic oils like peppermint and lemon are also derived from natural sources. On the other hand, synthetic flavours are artificially created and commonly found in powdered form, alcoholic solutions, or aqueous solutions. These synthetic options offer consistency and versatility in flavour profiles across a broad selection of products. Table 4 presents a list of both natural and synthetic flavouring agents and sweeteners used for taste masking.

According to a study of the tastes of all humans, sweet is highly agreeable to our species. For this purpose, several types of sweeteners are used. The widespread natural and artificial sweeteners utilised in medications, together with their comparative sweetness levels and pertinent comments, are presented in Table 5. The values presented as relative sweetness levels indicate how sweet each substance is compared to sucrose (table sugar), which serves as the standard with a sweetness level of 1. These levels are determined through sensory evaluation tests involving human taste panels. Participants taste solutions of each sweetener at different concentrations and compare them to a standard sucrose solution. The sweetness level is quantified by how much of the sweet-

ener is needed to achieve the same perceived sweetness as the standard sucrose solution. For example, a relative sweetness of 200 for aspartame means that aspartame is 200 times sweeter than sucrose, meaning much less aspartame is required to achieve the same sweetness level. The determination involves both controlled laboratory settings and statistical analysis to ensure accuracy and reliability in the perceived sweetness comparison. This method helps in identifying and quantifying the potency of various sweeteners, enabling their appropriate application in food and beverage formulations.

Aspartame is a common sweetener used for the reduction of bitterness. For bitterness reduction of 25% acetaminophen, a very small concentration (0.8%) is required. The US-FDA banned cyclamate in 1970 due to its carcinogenic activity. Neohesperidin dihydrochalcone serves as an artificial flavour enhancer and suppresses bitterness.

Table 5 Sweeteners commonly used along with their relative sweetness levels[113]

Sweeteners	Comparative sweetness level	Comment
Sucrose	1 (standard)	Most commonly used
Mannitol	0.60	Negative heat of solution
Lactose	0.16	High amount is required
Cyclamate	40	Banned
Glycerrhizine	50	Moderately expensive
Acesulfame potassium	137–200	Bitter in high concentration
Aspartame	200	Less stable in solution
Sucralose	600	Synergistic sweetening effect
Saccharine	500	Bitter in high concentration

Table 4 Different drug substance specific natural/synthetic sweeteners and flavours used for bitter taste masking

Drug substance	Sweeteners/flavouring agents	Evaluation method/study population	Ref.
Natural taste masking agents			
Azithromycin or clarithromycin	Mixture of dry syrup and acidic jellies	Taste sensor	88
Buprenorphine/naloxone	Menthol and sucralose	Healthy volunteers	89
Cefuroxime axetil	Stearic acid and sucrose	Dissolution, human volunteers	90
Bactramin C and polymyxin B sulfate	Food additive BMI-60	Adult and child volunteers	91
Dexamethasone	Thaumatin and sucralose	Breast cancer patients	92
Donepezil hydrochloride	Ammonium glycyrrhizinate	Human volunteers	93
Epinephrine	Citric acid	Electrical tongue	94
Propranolol hydrochloride	Simple syrup	Children	95
Midazolam	Strawberry syrup	Children	96
Midazolam	Sucrose and cyclodextrin	Solubility and dissolution	97
Probiotics and microbial food supplements	Tropical juices	Trained panel	98
Quinine, caffeine and salicine	Flavanones from Yerba santa	Panelists	99
Quinine hydrochloride	Sucrose	Taste sensor	100
Ginseng	Dark chocolate	Panelists	101
Quinine	Cocoa or chocolate-flavoured	Adult volunteers	102
Diclofenac	Mint, liquorice flavour and sucralose	Electrical tongue	103
Synthetic taste masking agents			
Chloroquine phosphate	Aspartam	Human panel	104
Ibuprofen		Dissolution test	105
Ondansetron		Human volunteers	106
Ranitidine HCl		Children and adults	107
Metformin	Acesulfame-isomalt	Self-made questionnaire	108
Quinine sulfate	Acesulfame potassium	Electrical tongue	109
Famotidine menthol (flavours)	Menthol (flavour), aspartame (sweetener)	Healthy volunteers	110
Polyphenols of olive leaf extract	Sucrose and sodium cyclamate	Trained sensory panel	111
Hydrocortisone	Neotame	Young healthy adults	112

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3.3. Taste masking by microencapsulation

Microencapsulation is crucial across industries like pharmaceutical, offering multiple advantages towards efficient drug delivery. Among these, coacervation-phase separation, fluidized bed, solvent evaporation, and spray drying, as well as spray congealing, stand out for their efficacy in taste masking. These techniques involve encapsulating active ingredients within a protective shell, ensuring taste neutrality or controlled release. Additionally, methods such as air suspension coating, pan coating, multi-orifice-centrifugal processes, and interfacial polymerization also contribute to diverse microencapsulation applications, each offering unique advantages tailored to specific product requirements. Microencapsulation involves enveloping tiny solid or liquid particles with polymeric materials or films, effectively preventing oxidation, volatilization, and masking of undesirable drug tastes.[114] The technique relies primarily on evaporation or solvent extraction principles, although variations such as spray drying and coacervation-phase separation are also employed for microencapsulation.[115]

Selecting the right polymer for microencapsulation is a complex task. The chosen coating polymer should hinder the release of the active ingredient in the mouth while facilitating release in the stomach or small intestine for absorption. An ideal polymer for taste masking should be insoluble in saliva with a pH value of 6.8, but should readily dissolve at a pH value of 1.2. Eudragit E, a commonly employed taste-masking polymer in microencapsulation, comprises butyl methacrylate, methyl methacrylate, and dimethylaminoethyl methacrylate. Characterized as a cationic polymer with a glass transition temperature of 48 °C, Eudragit E forms a permeable, insoluble, and swellable film at pH 5 or above, yet easily dissolves via salt formation at acidic pH levels below 5. This property allows Eudragit E to prevent drug release in saliva with a pH range of 6.8 to 7.4 while promptly dissolving in gastric fluid with a pH range of 1.0 to 1.5, making it a suitable choice for microencapsulation applications.[116] A few examples of taste-masked drug products developed by the microencapsulation technique are presented in Table 6.

Taste masking through microencapsulation covers bitter or unpleasant-tasting medications in a tasteless or pleasant-tasting coating, which has various benefits, including increased patient compliance, especially for paediatric and geriatric populations. By controlling the release rate and shielding the active ingredient from deterioration, this method improves the stability and bioavailability of the medication. Its drawbacks include higher production costs, possible manufacturing process complexity, and the possibility of changed drug release profiles in the event that encapsulation is not properly controlled. Regulatory obstacles and the requirement for comprehensive testing to guarantee the security and effectiveness of the encapsulated product may also arise.

3.4. Nanotechnology for taste masking

Nanotechnology has made remarkable strides in the field of taste masking, offering innovative solutions that were once beyond reach. Traditional methods of taste masking often involve using large quantities of excipients or sweeteners to cover up unpleasant flavours, which can alter the intended properties of a product. Nanotechnology, however, utilizes nanoparticles and nanostructures to provide a more sophisticated approach. By manipulating particles at the nanoscale, researchers can create highly effective taste-masking agents that operate on a molecular level. For instance, nanoparticles can encapsulate bitter or undesirable compounds, preventing them from interacting with taste receptors on the tongue. This encapsulation ensures that the unpleasant flavours are released only under specific conditions, such as during digestion, thus leaving the taste profile of the product intact. Moreover, nanotechnology enables the development of targeted release systems, where the taste-masking agent is designed to dissolve or degrade only at certain pH levels or temperatures, further enhancing the control over flavour perception. These advancements not only improve the palatability of pharmaceuticals and nutraceuticals but also have applications in the food and beverage industries, where they can create products with a more appealing taste without compromising on efficacy or safety. As research continues to evolve, the integration of the possibilities of product formulation paves the way for a new era of flavour management.[127] The details of various nanotechnology-based taste masking technologies for pharmaceuticals are described here.

Table 6 Example of taste masked drugs by the microencapsulation technique

Drug	Taste masking ingredient	Microencapsulation technique	Ref.
Atomoxetine HCl	Methacrylate copolymer	Fluidised bed	117
Diclofenac	Eudragit E	Fluidized bed	118
Berberine hydrochloride	Eudragit E	Fluidized bed	119
Naproxen sodium	Eudragit E	Fluidized bed	54
Lafutidine	Ethyl cellulose and hypermellose	Fluidized bed	9
Prednisolone	Eudragit E	Spray drying	120
Amlodipine and famotidine	Ethylcellulose	Spray drying	121
Sildenafil citrate	Eudragit E	Spray drying	53
Acetaminophen	Eudragit E	Spray congealing	122
Chlorpheniramine maleate	Chitosan/alginate	Ionotropic gelatin	123
Ciprofloxacin	Methacrylic acid divinyl benzene copolymer	Interfacial polymerisation	124
Drotaverine hydrochloride	Polyvinyl pyrrolidone	Solvent evaporation	125
Ondansetron hydrochloride	Eudragit E	Solvent evaporation	126

3.4.1.　Liposomal carriers for taste masking. The development of liposomal formulations has been very promising in overcoming the bitterness of poorly palatable drugs. For instance, mefloquine is an extremely bitter antimalarial drug that was encapsulated in liposomes to improve its acceptability for liquid pediatric dosage forms. Liposomal entrapment efficiently masked the bitterness of the drug, and the encapsulation was achieved by a solvent-assisted loading method that utilized an ammonium sulfate gradient. Liposomes were prepared using 1,2-distearoyl-*sn-glycero*-3-phosphocholine (DSPC) and cholesterol as lipid components.[128] The study also looked into the preparation of liposomes that carry loratadine and how they can help mask taste, achieve better solubilization, and improve its absorption in the body. Prepared using a phospholipid/cholesterol composition and thin-film hydration process, the study showed that liposomes acted as barriers and largely improved the bitterness of orodispersible loratadine and may work with better solubilization and absorption in the human body.[129] Additionally, caffeine, one of the most bitter drugs known, was loaded into chitosan-coated nanoliposomes, known as chitosomes. Chitosomes were prepared using a combination of lecithin, cholesterol, and polysorbate 80. After coating with chitosan on the outer layer, they are hydrated by the thin-film hydration method. The taste-masking efficiency was excellent compared to plain caffeine preparation, while the stability was superior to plain liposomes.

3.4.2.　Polymeric nanoparticles for taste masking. A novel taste-masked oral powder formulation of ibuprofen has been developed utilizing a polymeric nanoparticle approach *via* spray drying. It contains Eudragit L 100 (methacrylic acid–methyl methacrylate copolymer (1 : 1)) as the pH-sensitive polymer that will not dissolve at acidic pH, while the formulation includes PVP K30 and β-cyclodextrin. The prime aim here was to make the formulation as palatable and soluble as possible for the drug. The study emphasized that the ratio of the components like β-cyclodextrin and PVP K30 along with the methacrylic acid–methyl methacrylate copolymer relative to ibuprofen needs to be optimized to yield an effective formulation.[130] Saquinavir-filled nanoparticles were formulated for developing a pediatric oral formulation as a taste mask and stabilizer. Nanoparticles were prepared using interfacial polymerization incorporating a methacrylic acid–methyl methacrylate copolymer 1 : 2 (Eudragit RS 100), pullulan, and triglycerides produced from capric and caprylic acids. Nanoparticles were successful in reducing the bitterness of the compound, making it more appropriate for pediatric administration.[131]

3.4.3.　Solid lipid nanoparticles for taste masking. In a recent study, Zhang *et al.* prepared reverse solid lipid nanoparticles of atomoxetine hydrochloride for masking the bitterness of the active. The formulation process began with the preparation of plain liposomes, which were then mixed in equal proportions with a solution containing atomoxetine hydrochloride. It was then freeze-dried in a powder composed of the drug and phospholipid, followed by mixing in a medium chain triglyceride to produce an aqueous-clear sus-

pension. It effectively masked the bitterness of the drug.[132] Chao Li *et al.* prepared enteric-coated SLNs for enrofloxacin to increase its palatability, stability, and oral bioavailability. The SLNs were prepared using hot homogenization, followed by ultrasonic emulsification techniques with octadecanoic acid as the lipid matrix. Polyvinyl alcohol was used as an emulsifier and polyacrylic resin was used for enteric coating in this study. The research showed that these enteric-coated SLNs efficiently masked the bitter taste of enrofloxacin while increasing its stability and bioavailability.[133] Dandagi *et al.* prepared SLNs loaded with quinine sulfate to mask its very bitter taste. The lipid carrier used was glyceryl monostearate, while the surfactants were polysorbate 80, poloxamer 407, and poloxamer 188. The results showed that SLNs are highly effective in taste masking and made quinine sulfate tolerable for administration purposes.[134]

3.4.4.　Taste masking by nanostructured lipid carriers. Akhoond Zardini *et al.* prepared nanostructured lipid carriers (NLCs) in order to improve the solubility and hide the bitterness of lycopene. Ultrasonication in combination with a high-shear homogenization technique was used for NLC preparation. Glyceryl monostearate and glyceryl distearate served as solid lipid precursors, whereas caprylic/capric triglyceride served as a liquid lipid precursor. Co-surfactants that are used in this study for stabilization purposes include Tween 80 and lecithin. The lycopene-loaded NLCs, when added to orange juice, successfully masked the characteristic bitterness of lycopene and improved its solubility, rendering it organoleptically acceptable.[135]

3.4.5.　Polymeric micelles and taste masking. Li *et al.* investigated the potential of amphiphilic block copolymers as micelle-forming agents for taste masking in aqueous solutions. The study tested the ability of four water-soluble bitter drugs—berberine hydrochloride, quinine sulfate, gentopicroside, and matrine—to be masked by amphiphilic block copolymers. The specific copolymers used were mPEG2000-PCL2000, mPEG2000-PLLA2000, PLLA2000-PEG2000-PLLA2000, and mPEG2000-PLGA50/502000. The results demonstrated that these copolymers could effectively encapsulate the bitter drugs, reducing their bitter taste in aqueous solutions.[136]

3.4.6.　Taste masking by reverse micelle nanoparticles. Huang *et al.* developed a taste masked azithromycin formulation by using freeze-drying method-based reverse micelles. In this approach, phospholipids and azithromycin were mixed in medium-chain triglycerides and then lyophilized to obtain the dried powder. The drug was encapsulated within lecithin micelles in the medium-chain triglyceride matrix, creating a physical barrier for the API and isolating the drug from taste receptors. The study inferred that the reverse micelles effectively masked the bitter taste of azithromycin, making it more palatable.[137]

3.4.7.　Taste masking by nanosponge technology. Omar *et al.* fabricated nanosystems (NSs) of griseofulvin using cyclodextrin to improve its bioavailability and also to improve the taste of the developed formulation. Three different plain β-cyclodextrin nanosystems were prepared using a reaction

based on cross-linking, where β-cyclodextrin was cross-linked with diphenyl carbonate (DPC) in the presence of ultra-sonication. This approach aimed to enhance the solubility, taste masking, and bioavailability of griseofulvin.[138]

3.4.8. Taste masking by nanohybrid technology. An inorganic clay, montmorillonite (MMT) intercalated sildenafil (SDN), as a nanohybrid system was developed for taste masking. After intercalation, the nanohybrid system of SDN-MMT was coated with polyvinylacetal diethylaminoacetate (AEA), a basic polymer. The AEA-coated SDN-MMT nanohybrid exhibited slower dissolution at neutral pH when compared with a marketed sildenafil formulation, Viagra® tablet. This reduced dissolution resulted in minimum exposure of the drug to taste receptors in the mouth, thereby improving the taste experience in the buccal cavity.[139]

3.5. Taste masking by complexation (inclusion complexation)

To mitigate the perception of bitterness, the complexing agent can achieve its goal by either diminishing the oral solubility of the drugs post-consumption or reducing the exposure of taste buds to the drug particles.[16] Low-dosage drugs are the most suitable for this strategy. Due to its ability to create inclusion complexes with a range of molecules without covalent bonds, cyclodextrin is the most commonly used complexing agent for inclusion-type complexes. It is a cyclic oligosaccharide that is sweet, non-toxic, and made from starch.[140,141] A list of formulations in which complexation-based taste masking technology was applied for better formulation development is presented in Table 7.

There are a number of benefits and drawbacks to taste masking by complexation, especially when it is achieved through inclusion complexation. Its ability to successfully cover up the bitter taste of medications without appreciably changing their pharmacological characteristics is one of its main advantages. This method isolates the bitter or unpleasant taste from the taste buds by trapping the drug molecules inside the cavity of cyclodextrins or other appropriate complexing agents. This can improve adherence to treatment, particularly in the case of younger and older patients who are frequently sensitive to bitter drugs. Additionally, inclusion com-

plexes can increase some medications' solubility and stability, which may increase their bioavailability. There are a few disadvantages of this strategy, though. The size and compatibility of the drug molecule with the complexing agent, which may not be appropriate for all drugs, can restrict the formation of inclusion complexes. Furthermore, the procedure might necessitate complex manufacturing methods and be expensive. Additionally, there is a chance that the drug's release rate from the complex may be impacted, which could have an effect on the medication's effectiveness.

3.6. Taste masking by granulation

Granulation stands out as a cost-effective, rapid, and easily scalable method for taste masking. In this approach, bitter-taste drugs are combined with flavours, waxes, and polymers, serving as granulating agents. During the granulation process, taste masking can be achieved using liquid and low melting point waxes, such as glyceryl behenate, glycerol palmitostearate, and hydrogenated castor oil. The formulation of taste-masked oral solid or liquid dosage forms involves processing mixtures of bitter drugs, hydrophobic polymers, sweeteners, lipids, or waxes through dry, wet or melt granulation techniques. Granulation effectively reduces the exposure of the bitter component to the tongue upon oral consumption, yet the extent of bitterness masking may vary. Nevertheless, taste-masked granules incorporating saliva-insoluble polymers can be formulated into various tablet forms, including rapidly dissolving tablets and chewable tablets.[147] To mask the taste of calcium-containing substances like calcium carbonate, melt granulation is used. The granules produced by melt granulation have a calcium-containing substance with a sugar alcohol as a binding agent and have a pleasant taste and mouth feel. To enhance the effectiveness of taste masking, sugar alcohols, flavours, and other ingredients are also added to the mixture. Various examples of taste masking of bitter drugs by using the granulation technique are presented in Table 8.

Granulation or coating the active pharmaceutical ingredient (API) inside granules improves palatability by delaying the patient's perception of an unpleasant taste. This approach has the potential to improve the stability and controlled release of

Table 7 Taste masking of bitter drugs by complexation

Drug	Complexing agent	Dosage form	Ref.
Carbepentane citrate	Cyclodextrin	Oral liquid	7
Benexate hydrochloride	Cyclodextrin	Granules	7
Ibuprofen	Hydroxy propyl-β-cyclodextrin	Solution	7
Chloroquine phosphate	Tannic acid	Syrup	142
Gymnema sylvestre	Chitosan	Oral liquid	7
Dimenhydrinate	Eudragit S-100	Chewable tablet	143
Benzethonium chloride	β-Cyclodextrin	Mouthwash	140
Dioscin	β-Cyclodextrin	Solid oral	144
Benexate	β-Cyclodextrin	Powder	140
Hexitidine	HP-β-cyclodextrin	Aqueous solution	140
Acetaminophen	β-Cyclodextrin	Pellet	145
Pinaverium bromide	β-Cyclodextrin	Tablet	145
Libexine HCl	β-Cyclodextrin	Oral solid	145
Metronidazole benzoate	γ-Ccyclodextrin	Aqueous solution	146

Table 8 Taste masking of the bitter drugs by using a granulating agent[148]

Drug	Granulating agent	Category
Alprazolam	Eudragit E 100	Anxiolytic
Clopidogrel sulphate	Sugar alcohol, castor oil	Antiplatelet
Calcium compound	Sugar alcohol	Mineral supplement
Dextromethorphan	Cyclodextrin	Antitussive
Erythromycin	Alginic acid	Macrolide
Granisetron HCl	Glycerol palmitostearate or glyceryl stearate	Antiemetic, anti-nauseant
Ibuprofen	Microcrystalline cellulose (MCC)	Anti-inflammatory
Levofloxacin	Sugar alcohol, castor oil	Fluoroquinolone antibiotic
Macrolide antibiotic	Polycarbophil	Macrolide
Ondansetron	Polacrillin potassium	Anti-nauseant, antiemetic
Penicillin and macrolide	Wax or hydrogel	Antibiotics
Pristinamycin and telithromycin	Beeswax or glyceryl stearate	Macrolides
Vitamins	Polyglycerol ester of polyvalent fatty acid	Diet supplement

the API, and it also improves patient compliance, particularly in children and those having high sensitivity towards odd tastes. Nevertheless, drawbacks include higher production costs and complexity, possible difficulties maintaining consistency and uniformity in taste masking, and the potential for partial taste exposure due to granules' residual release of the API in the mouth.

3.7. Taste masking by ion exchange resin complexation

Ion-exchange resins (IERs) are characterized by high molecular weight polymers featuring both anionic and cationic functional groups. These cross-linked polyelectrolytes are water-insoluble and possesses numerous binding sites, thus exhibiting a high capacity for drug loading. Cation and anion exchange resins represent the two primary classifications of ion exchange resins based on the charge carried by their functional groups. Within each category, they are further categorized as strong or weak, depending on their affinity for counter ions. Anionic resins primarily exchange chloride ions, whereas cation exchange resins typically exchange sodium, potassium, or aluminium salts. For the drug loading on resins, both column and batch methods are used.[144] IERs, through weak ionic bonding with oppositely charged drug molecules, form insoluble resonates. After ingestion, in the digestive system, resin exchanges the drug with a counter ion and the drug is eluted and absorbed. IERs like amberlite are used in taste masking of dextromethorphan and made into fast-acting and oral films. To produce the best taste masking agent, the right and careful selection of IER is necessary. Along with the resin's biocompatibility and biodegradability, the concentration of the exchangeable group, adequate functional group, and swelling ratio determine the choice. IERs are mainly classified into four groups: strong acid cation resins (including sulphuric acid species like indion 244, amberlite IRP-69, amberlite IR-120, and tulsion T-344) can be used to mask the taste of basic drugs, because they work across the full pH range; weak acid cation exchange resins like Amberlite IRP-64, Tussion T-335 and Indion 204 with carboxylic acid moieties are still functional above pH 6.0; strong base anion exchange resins like Amberlite IRA-400 and Indion 454 with quaternary amine ionic sites are used to mask the taste of acidic drugs

and they are functional across the full pH range; and tertiary amine substituted weak base anion exchange resins like Amberlite IRC-718 are effective well below pH 7.0.[149] Various examples of taste masking by ion exchange resins are given in Table 9.

Ion exchange resin complexation for taste masking has a number of benefits and drawbacks. One important benefit is that it binds the active pharmaceutical ingredients (APIs) to the resin, preventing them from interacting with taste buds and effectively masking the taste of bitter drugs. This approach is flexible and can be applied to a variety of medications, improving patient adherence, particularly in the case of younger and older patients. Furthermore, controlled release of the API can be achieved with ion exchange resins, enhancing therapeutic efficacy. Nevertheless, there are drawbacks that could affect the medication's overall efficacy, such as the possibility of drug–resin complexes having reduced bioavailability and slower drug release rates. In addition, there may be difficulties with the stability and compatibility of the drug–resin complexes with other formulation elements, as well as a complex and expensive manufacturing process.

3.8. Taste masking by prodrugs, salts or derivatives

Prodrugs are frequently used to mask the taste of bitter substances by decreasing the solubility of the drug in saliva and/or decreasing the affinity of the drug for receptors. The bitter taste commonly associated with opioid analgesics and antagonists is mitigated by employing the buccal distribution technique, which enhances bioavailability compared to oral administration. Notably, several prodrugs of naltrexone, naloxone, nalbuphine, oxymorphone, butorphanol and levallorphan exhibit a lack of bitter taste due to esterification of the 3-phenolic hydroxyl group. This modification renders these compounds more palatable and improves patient compliance. It was concluded that changes in taste were not due to variations in water solubility and that the phenolic functional group is important when interacting with taste receptors. As a result, buccal administration of the synthetic prodrugs of these substances increased bioavailability in comparison with oral administration without the typical bitter taste. Karaman and co-workers developed prodrugs to disguise the unpleasant

Table 9 Taste masking of bitter drugs using ion exchange resins

Drug	Category	Commercial resin used	Ref.
Azithromycin, metronidazole, Quinine sulphate, erdosteine, Paracetamol,	Macrolide, antiprotozoal, antimalaria, mucolytics, analgesics	Dowex 2, Amberlite IR 4B	150
Buflomedil	Vasoactive agent	Amberlite IRP 69	151
Clarithromycin	Macrolide antibiotic	Carbomer 934	144
Chlorpheniramine maleate	Antihistamines	Indion CRP 254, Indion CRP 244	152
Clopidogrel sulphate	Antiplatelet drug	Water soluble cation exchange resin with sulfonic acid groups	153
Ciprofloxacin	Fluoroquinolones	Lewatit CNP, Indion 234	154
Chloroquine phosphate	Antimalarial	Indion cation exchange resin	155
Dextromethorphan hydrobromide	Antitussive	Carbomer 934, Amberlite® IRP-69	156
Donepezil chloride	Anti-Alzheimer's drugs	PVP and anionic polymer	157
Erythromycin	Macrolide antibiotic	Carbomer 934	158
Ephedrine hydrochloride	Sympathomimetic drug	Indion CRP 244/254	148
Erythromycin stearate	Macrolide antibiotic	Dowex 50, Amberlite IR 120, Indion 244	148
Orbifloxacin	Fluoroquinolone antibiotic	Amberlite IRP 64/69	148
Paroxetine hydrochloride	Antidepressant	Amberlite IRP 88	148
Remacemide hydrochloride	Anti-Parkinson's drug	Amberlite IRP 64	148
Ranitidine hydrochloride	Antihistamines	Amberlite IRP 69/88	148
Spiramycin, roxithromycin, dimenhydrinate, norfloxacin, ofloxacin, levocetrizine	Macrolide antibiotic, antihistamine, antibiotic, Antihistamine	Kyron-T-104, Purolite C 102 DR, Amberlite IRP 50, Doshin P 544(R), Indion 204	159

taste of several medications such as atenolol, pseudoephedrine, dopamine, cephalexin, amoxicillin, and cefaclor. The linker's role in these prodrugs is to prevent the free amine group from forming in the parent compound while maintaining the release of the drug in a controlled manner.[160–162]

Converting a water-soluble drug into a less water-soluble salt form is another taste-masking technique. The formation of salt makes drugs tasteless and also decreases the solubility of the drug and reduces its solubility in saliva. Chloramphenicol's strong bitterness is a significant drawback when used in paediatric formulations. Chloramphenicol palmitate (CP), a sparingly soluble ester form, is essentially tasteless due to its limited aqueous solubility. Pancreatic lipase readily hydrolyses the type of chloramphenicol palmitate that is used in drugs to form active chloramphenicol.[163] Another approach was used for masking the bitterness of propiverine HCl; it was desalinated to create a propiverine-free base, which was then formed into fine granules. The free base fine granules and tablets of propiverine HCl dissolve at about the same rate and have nearly the same bioavailability as the original drug.[164]

Prodrugs, salts, or derivatives have a number of benefits and drawbacks when it comes to taste masking. Prodrugs are pharmacologically inert derivatives that the body transforms into active medications and these have the potential to greatly lessen unpleasant tastes and improve patient compliance, particularly in the elderly and paediatric populations. Salts have the ability to change a drug's stability and solubility, which may enhance its flavour and palatability in general. Without compromising the medication's ability to work as intended, derivatives can change the chemical structure to reduce bitterness. These approaches do have drawbacks, though, as prodrugs need metabolic conversion, which varies from person to person and may result in uneven drug efficacy. Salt formation may have an impact on how well the medication is absorbed

or cause new side effects. Derivative creation may require intricate chemical synthesis, which raises production costs and duration.

3.9. Taste masking by solid dispersion

The technique of distributing or dispersing a drug throughout a dispersion medium is known as solid dispersion. Normally, the medium is molten or a polymer solution. Either the molten mixture can be solidified or the solvent can be evaporated to create the drug-containing granules. There are various techniques for the preparation of solid dispersions. Spray congealing is a technique that is typically used to modify the structure of materials to produce masked pellets with sizes ranging from 0.25 to 2.0 mm and free-flowing powders from liquids. The drug is allowed to melt, dissolve or disperse in a heated melt of additional additives throughout this process. To produce spherical congealed pellets, it is then sprayed into an air chamber where the temperature is below the melting point of the formulation ingredients. Beeswax and water-insoluble polymers like ethylcellulose are generally used for this purpose. Solid bonds created from the congealed melts keep the particles together. Most spray congealing procedures do not involve solvent evaporation; therefore, the particles are typically robust and non-porous, holding together when agitated. The properties of the final spray congealed product depend on the properties of the material used. Poorly soluble drugs can be made more soluble by specific interactions with hydrophilic polymers, and *vice versa* with reliable interactions between the drug and hydrophobic polymers. Francese and coworkers (1995) reported a drug–polymer matrix composition to achieve the taste masking of dimenhydrate. Shellac, cellulose acetate phthalate, and zein are examples of copolymers whose esters and carboxylic acid groups may interact physically and chemically with the dimenhydrinate's amine or amido group.[165]

There are a number of benefits and drawbacks of taste masking by solid dispersions. By encasing drugs in a polymer matrix that keeps the drug from dissolving in the mouth and thereby lessening its taste, solid dispersions can effectively mask the unpleasant taste of drugs. Patient compliance can be increased with this strategy, particularly in the case of younger and older patients. Furthermore, poorly water-soluble drugs' solubility and bioavailability can be improved by solid dispersion technology. Nevertheless, there are disadvantages as well, like the difficulty of the manufacturing process, possible problems with the dispersion's stability over time, and the potential for insufficient taste masking if the medication is released too soon. Furthermore, choosing the right carriers and processing parameters can be difficult and necessitate thorough formulation.[166]

3.10. Rheological modification

Decreasing the diffusion of bitter compounds from the saliva to the taste buds can be accomplished by increasing the viscosity with rheological modifiers like carbohydrates or gum. To minimize the strong bitter taste of acetaminophen solution, it can be made with MCC (microcrystalline cellulose) (0.6–1%) and xanthan gum (0.1–0.2%). Phenobarbital and acetaminophen syrup have a bitter taste masked by a polyhydric alcohol like polypropylene glycol or polyethylene glycol with gelatin and polyvinyl pyrrolidone. Mirtazapine, an antidepressant, is manufactured as an aqueous suspension utilizing maltitol as a thickener and methionine as a stabiliser. Maltitol masks the drug's undesirable taste, while inhibiting its unfavourable local anaesthetic action. It is stable in the acidic pH range of 2 to 3. The astringent taste of tannic acid is concealed by the presence of flavouring agents and gelatin by inducing the jelling effect upon cooling.[167]

3.11. Taste masking by fast-dissolving approaches

Orally disintegrating tablets (ODTs), often called fast-dissolving dosage forms (FDDFs), are a recent and effective technical advancement for masking bitter taste. ODTs are preferred over the conventional tablet forms as they disintegrate and dissolve readily in the saliva without water. ODTs, as new dosage forms, have several distinctive characteristics that set them apart from more conventional ones. ODT formulations' primary advantage is combining the benefits of both liquid and conventional tablet dosage forms. Children and the elderly can consume ODTs more easily because they do not have to take the medication with water. The development of a suitable ODT requires careful consideration of taste masking. Sweeteners and flavours are currently used as taste masking agents in some fast-dissolving/disintegrating tablet formulations. However, these are insufficient tools for masking the taste of a variety of bitter drugs. The process of compaction is another significant challenge when dealing with coated drug particles. ODT technology's low compaction force is useful for masking the bitter taste of medicine since it reduces the chance of breaking of the barrier coat during compression. Adsorption onto or complexation with carriers and spray coating of drug particles are the two main techniques for masking taste. In addition, ODTs use modern methods including spray drying, freeze-drying, moulding, spinning, sublimation, effervescence and sintering. Certain excipients can also be added like sugars, calcium salt and disintegrants, in addition to compression techniques that are widely used. Below is a brief description of a few of the FDDF technologies.

A FDDF tablet called Zydis® (Cardinal Health) is manufactured by lyophilizing or freeze-drying the drug in a matrix that typically contains flavours, gelatin and sweeteners to improve the dosage forms' taste. A frozen drug suspension or solution that contains excipients forms structures upon solvent removal. In 2 to 3 seconds, it dissolves on the tongue. Additionally, it includes complexation with ion exchange resins or microencapsulation using specialized polymers to mask the bitterness of the drugs.[160] Another fast-disintegrating/dissolving dose form is OraSolv® (Cima Labs). A very slight effervescence helps the OraSolv technology deliver in the saliva. The tablet matrix dissolves in less than a minute, and the tablet matrix dissolves, leaving the coated drug powder behind. The OraSolv formulation uses a dual approach to taste masking; in addition to sweeteners or flavours, this technology also uses drug powder coating and effervescence to disguise the drug unpleasant taste. A second-generation fast-disintegrating/dissolving tablet formulation is called DuraSolv® (Cima Labs). It is manufactured in a process similar to OraSolv®, but higher compaction pressures were used during tableting; it has a substantially higher mechanical strength. Many FDDF formulations are available to mask the taste of bitter drugs, including Ceform™ (Biovail), FlashTab® (Ethypharm), EasyTec™ (Antares Pharma) and Oraquick® (KV Pharmaceuticals).[159] Various examples of taste masking by commercially available fast dissolving dosage forms are given in Table 10.

4. Factors affecting the taste masking approaches

There are various factors affecting the selection for taste masking approaches like the dose of the API (active pharmaceutical ingredient), extent of bitter taste, drug solubility, drug particle size and size distribution, dosage form and ionic properties of the drug.

4.1 Dose of APIs

The dose of a drug may determine the most effective formulation approach for achieving taste masking. In paediatric formulations, the dose is often small enough to permit the use of flavouring additives to mask the taste of the drug. For instance, sweeteners were employed to create a palatable oral formulation of low-dose paediatric aspirin. However, due to the significant quantity of acetaminophen involved, the same strategy proved ineffective in mitigating the taste issue. In such cases, a coating with sweeteners is preferred to ensure taste masking and an appropriate final dosage form size.[16]

Table 10 A few commercially available fast dissolving dosage forms with taste masking technology

Drug	Product FDDF	Indications	Company name	Ref.
Acetaminophen caffeine	Excedrin® QuickTabs™	Pain reliever	Ethypharm – BMS	168
Acetaminophen	Tempra® FirsTabs	Paediatric analgesics	CIMA – Med Johnson	169
Acetaminophen	Tylenol®	Headache	McNeil PPC	170
Acetaminophen, dextromethorphan, pseudoephedrine	Triaminic® SoftChews®	Throat pain and cough	CIMA – Novartis Consumer Health	171
Diphenhydramine citrate	Benadryl® Fastmelt™	Antihistamine	Yamanouchi – Pfizer	—
Famotidine	Pepcid RPD®	Heartburn	Merck & Co., Inc.	172
Hyoscyamine sulfate	NuLev™	Irritable bowel syndrome	CIMA – Schwarz Pharma	173
Loratadine	Dimetapp®	Antihistamine	Wyeth	174
Loratadine	Claritin® RediTabs®	Antihistamine	R.P. Scherer – Schering Plough	175
Mirtazapine	Remeron® SolTabs™	Depression	CIMA – Organon	176
Ondansetron HCl	Zofran®	Nausea and vomiting	R.P. Scherer – Glaxo SmithKline	177
Olanzapine	Zyprexa® Zydis®	Schizophrenia	R.P. Scherer – Eli Lilly	178
Rizatriptan benzoate	Maxalt® MLT	Migraine	R.P. Scherer – Merck	179
Zolmitriptan	Zomig® ZMT and Rapimelt	Migraine	CIMA – Astra Zeneca	180

4.2 Drug particle size and size distribution

The efficiency of the taste-masking technique would depend on the properties of the drug particles. Poor taste masking efficiency and uneven dissolution of coated particles are caused by core materials with irregular shapes and small particle sizes. Taste masking through coating can be ineffective due to issues such as abrasions, the formation of dusty particles, and inconsistent coating thickness. Such coating defects can be minimized or completely eliminated by using a multilayer coating with an inner spacing layer that differentiates the drug from a taste-masking layer. Gatifloxacin and dextromethorphan taste-masked granules were manufactured using a layered coating with an inner spacing layer and an outer taste-masking layer.

4.3 Extent of bitter taste

Even a small amount of exposure is enough to detect an awful taste in medicines with an aggressively unpleasant flavour. In one example, due to ibuprofen's dominating taste, sweeteners were unable to mask the taste of its oral formulation. For aggressively bitter drugs, coating is a more efficient approach; even coating defects occur that reduces efficiency of the technique. Similar to this, liquid oral suspensions cannot mask their taste by microencapsulation of extremely bitter APIs like azithromycin. Viscosity modifiers are used to improve taste masking efficiency. Viscosity enhancers in oral suspensions can mask the unpleasant taste arising from drug leakage from coated drugs or microcapsules. The taste masking of bitter drugs like etoricoxib, celecoxib and quinine and of antibiotics like ofloxacin, ciprofloxacin, levofloxacin, cefuroxime axetil, clarithromycin and erythromycin is difficult by using conventional taste masking techniques like sweeteners, amino acids, and flavouring agents.[181]

4.4 Drug solubility

The physicochemical characteristics of the drugs are crucial when choosing a taste-masking technology. For example, sodium bicarbonate (alkalizing agent) was added to a fast disintegrating ondansetron composition to decrease the water solubility and the resulting gustatory perception because ondansetron has a con-siderably poor water solubility at higher pH levels. Efficiently masking the bitter taste associated with a poorly soluble form of ranitidine can be achieved through the lipid coating of the drugs. If the product is produced using an aqueous medium, conventional lipid coating of the drug component for ranitidine water-soluble forms (such as ranitidine hydrochloride) may not sufficiently achieve the desired degree of taste masking. In order to effectively mask the taste, ranitidine hydrochloride was first added to the inner core of a polymeric binder, a lipid, or wax that has a higher melting point than the outer coating.[148]

4.5 Dosage forms

According to estimations, children and about 50% of aged people have trouble swallowing tablets. These issues have been addressed with liquid oral dosage forms and chewable tablets. However, a few drugs are challenging to formulate in these dosage forms due to their unpleasant taste. For formulations meant to be ingested whole without chewing, capsules, coated tablets, and slowly disintegrating hard tablets stand as the favoured taste-masking technologies. Alternatively, taste masking in liquid oral formulations can be achieved through various methods including particle coating, sweeteners, granulation, and microencapsulation. Chewable tablets also benefit from these technologies, complemented by viscosity enhancers and pH modifiers.[148]

4.6 Ionic properties of the drug

The suitability of drug candidates for ion exchange resin polymers, along with the selection of appropriate polymers, hinges on the ionic properties of the pharmaceuticals. Specifically, cationic polymers are well-suited excipients for anionic drugs such as sildenafil, while anionic polymers are preferable for cationic drugs like donepezil hydrochloride.[182]

5. Evaluation tests

In the pharmaceutical industry, evaluating taste masking substances is crucial, particularly for orally delivered drugs that
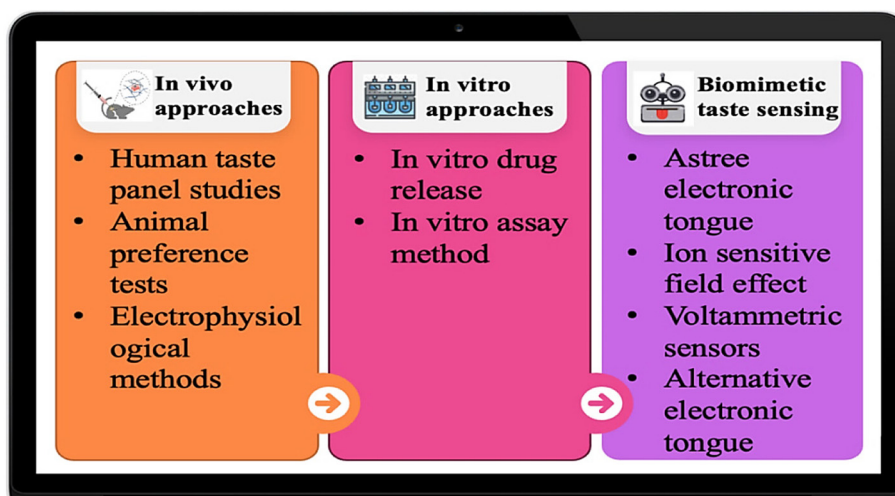
Fig. 4 Types of evaluation tests for the determination of taste masking efficiency.[183]

could have unpleasant tastes. A flavour masking agent's potency can be evaluated using a variety of tests and methods. Some specific tests and methods frequently employed for assessing taste-masked substances are given in Fig. 4.

5.1 Electronic tongue

When combined with data from human taste assessments, electronic tongue or taste sensors are tools that are trained to quickly screen the flavour qualities of formulations. Application of the electronic tongue requires test chemicals to be sufficiently soluble in water. Co-solvents like ethanol can be employed to make test substances more soluble and to expand the scope of an instrument's application. These devices share a common structure of three main parts: a sensory array, signal-emitting and receiving hardware, and pattern recognition software. Recent years have seen the development of three different types of devices known as electronic tongue, or taste sensors, based on potential, impedance spectroscopy, and voltammetry. Iiyama and co-workers introduced the potential-based gustatory sensors initially. It is made up of several lipid types and polyvinylchloride (PVC) membranes that convert taste quality information, such as salty and bitterness, into electrical signals.[184] Another type of prospective taste sensors was described by Vlasov and co-workers, which was built by numerous non-specific sensors based on chalcogenide glasses as transducers.[185] The second electronic tongue, which was based on impedance spectroscopy, was initially reported by Riul and co-workers, who used impedance spectroscopy to analyse sensors made of supramolecular thin films of conducting polymers and lipid-like material. Winquist and co-workers created the third type, which was based on the voltammeter idea. It comprises a number of metallic electrodes (Ag/AgCl reference electrode and stainless steel counter electrode, and platinum, gold, palladium, iridium, rhenium, and rhodium) that function as working electrodes. Electronic tongues can analyze and compare the flavour profiles of food products, ensuring consistency in taste. For example, they are used in

the beverage industry to maintain the same taste in different batches of wine or coffee. Electronic tongues are used to detect biomarkers in body fluids, such as saliva which can indicate the presence of diseases like diabetes or infections. During the drug development process, electronic tongues help in formulating drugs that are both effective and have a pleasant taste, improving patient compliance.[186]

Method development and process validation are essential for the effective use of an electronic tongue. Method development involves establishing analytical procedures to ensure that the electronic tongue can accurately and reliably identify and quantify different taste profiles. This includes selecting appropriate sensors, calibrating the device, and optimizing operational parameters. Process validation is crucial to confirm that the electronic tongue consistently produces accurate results under varied conditions, ensuring reproducibility and robustness. This involves rigorous testing and documentation to demonstrate the reliability and accuracy of the system in detecting specific analytes in diverse sample matrices, thereby ensuring that the technology meets regulatory and quality standards.[187]

5.2. Instrumentation

A sample table, an amplifier, a computer for data storage, various sensor types attached to an arm, and an electronic taste-sensing system are its major components. A simple explanation of the electrochemical taste-sensing mechanism is provided in Fig. 5.

This technology mimics what happens when molecules with particular tastes interact with taste receptors on the tongue. Taste buds are represented by sensors that engage with these chemicals at their surface and cause potential modifications. These signals are compared to action potentials that correspond to brain network activity at the physiological level, which are recorded by computers. The collected data can also be assessed using a matrix of sensor responses that has previously been created and can be compared to human
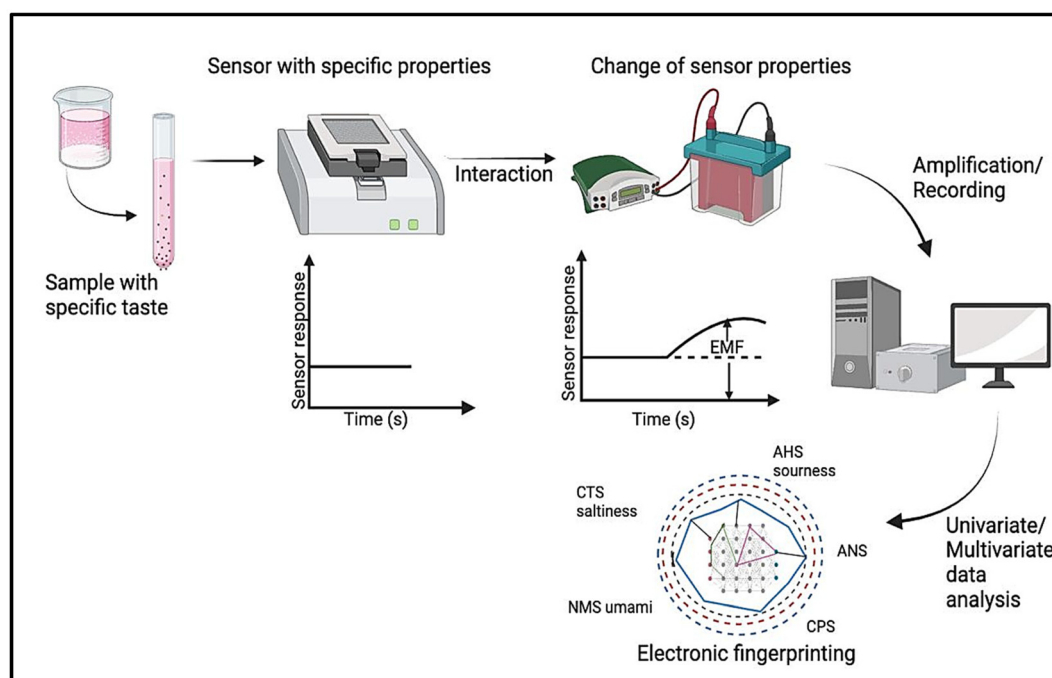
Fig. 5 Schematic representation of an electronic taste conveying system for identifying the degree of taste masking.[188]

memory or associations with known flavour patterns. Potentiometry is the principle that is used the most. Here, the taste sensing principles of major existing technologies are discussed in more detail.

5.3. Electrochemical concept

The concept of synthesising the human response to external stimuli was first proposed in the year 1943.[188] In order to create an "electronic brain" and artificial intelligence based on neural computing, this concept has been expanded. An "electronic nose" (1982) used for gas analysis was the first analytical tool based on these notions.[189] A promising tool for both quantitative and qualitative analysis of multi-component matrices is the "electronic tongue," which was first introduced in 1995.[190] According to the literature definition, "the electronic tongue is an analytical instrument comprising of an array of nonspecific, low-selective chemical sensors with high stability and cross-sensitivity to different species in solution, and an appropriate method of pattern recognition (PARC) and/or multivariate calibration for data processing".[191]

The application of a variety of nonspecific or low-selective sensors to provide signals during sample analysis is the general idea of the electronic tongue utilised for analysis. The concept behind adopting low-selective sensors is based on an analogy to the biological structure of mammalian taste systems. There are millions of non-specific receptors that respond to various chemicals in the tongue region. On the tongue of mammals, there are many dozens of taste receptors. The brain receives the taste signals from the receptors and processes them *via* a network of neurons. As a result, the sensed object's image is produced.

6. Regulatory perspective

With the adoption of pediatric regulations in the USA and EU, the demand for age-appropriate medicines for children has significantly increased. The economic impact of poor medication adherence is immense, with inadequate adherence leading to an estimated 125 000 deaths annually in the U.S. alone. According to the European Medical Association (EMA) in 2006, the taste, smell, and texture of medications play crucial roles in their accessibility and acceptability by patients. In 2015, the EMA emphasized concerns regarding the modification of pediatric doses, by incorporating them into soft foods or altering them before administration. They highlighted potential impacts on quality, efficacy, and safety, underscoring the importance of proper dosage administration.[192] Regional regulations on taste masking may differ; however, the following general guidelines and considerations are usually followed, *i.e.*, safety and efficacy, formulation, patient compliance and palatability, stability and shelf life, bioavailability, quality control, paediatric use, labelling and packaging, clinical studies, and regulatory approval. Palatability and swallowability are important factors in determining a patient's acceptance of a medication as they impact adherence. One way to describe a drug product's characteristics is its palatability. That improves its flavour, texture, aftertaste, fragrance and acceptability and is an important component in deciding whether patients will accept oral dose formulations. It is possible that swallowability characterized the patient's ability to swallow the medication without choking or gauging. Taste perception develops from a young age and changes as a person ages. Usually, the objective should be drug formulations that most

patients would find acceptable and that have a neutral taste. Pharmaceutical companies should work closely with regulatory agencies and consult the latest guidelines to ensure compliance when developing taste-masked drug products. The safety as well as efficacy of the medications are the main concerns of regulatory bodies like the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA).[193] When considering drug applications, regulatory bodies may consider the effect of taste masking on patient compliance. The drug's bioavailability should not be adversely affected by taste masking. Regulatory bodies may ask for studies or data to show that the taste-masking formulation does not affect drug absorption or pharmacokinetics. Throughout the drug's shelf life, the taste-masking composition should remain stable. Stability data must be provided to show that the taste masking does not compromise the product's integrity. Validating analytical methods is necessary to confirm taste masking efficacy. Taste-masked drug labelling and packaging provide clear instructions to patients and healthcare providers on administration and dosage. Regulatory bodies frequently require paediatric taste studies to ensure that taste masking is effective and acceptable to the target age group. As part of the drug approval procedure, pharmaceutical companies are required to apply for regulatory approval of taste-masked formulations. A new drug application (NDA) or equivalent regulatory submission is often required for this.

7. Future perspective

The pharmaceutical industry is actively developing new medications for children, promising to introduce vital innovations and close the current gaps in the availability of suitable formulations for young patients. This endeavour is set to enhance the future landscape of paediatric healthcare by addressing the burning issues to improve oral pediatric dosage forms. Optimizing these formulations to be easy to swallow, palatable, and available in suitable dosage units will significantly enhance clinical care for children and benefit many adults as well. A key challenge in this area is the bitter taste of many pediatric medications, which necessitates effective strategies to improve palatability. Current methodologies, such as the use of sweeteners, flavourings, and sophisticated formulation techniques, are being employed to address bitterness. However, future efforts should focus on pioneering new taste-masking technologies and exploring alternative delivery systems like dissolvable films and chewable tablets. Moreover, understanding pediatric dosage form preferences according to specific age and developmental stages, along with validating and cross-validating taste preferences with adult panels, is crucial. Investigating the genetic determinants of taste perception in children can also lead to formulation innovations that prioritize safety, efficacy, and palatability. To achieve these goals, fostering collaborations between researchers and pharmaceutical developers, investing in patient-centred research to comprehensively grasp children's taste preferences, and advocating for regulatory guidelines that emphasize the importance of taste in paediatric medication adherence are essential. Ultimately, enhancing the palatability of paediatric medications will optimize compliance and therapeutic outcomes to grasp the treatment goals for pediatric population.

8. Conclusion

Adherence to medication is significantly affected by how it tastes. Bitter-tasting drugs can be particularly challenging for patients, leading to poor compliance, and even can influence the treatment goal. Improving the acceptability of such bitter tasting medicines by taste masking technology is promising towards improving therapeutic outcomes. Several approaches discussed in this article have been extensively explored on a case basis to enhance the adequacy of such pharmaceutical products; however, there is still a large scope for research in this segment of drug formulation development. The sophisticated approaches described herein are specially beneficial for target patient populations like pediatric and geriatric patients who may have difficulty in swallowing or tolerating unpleasant tastes. For effective taste masking, it is essential to understand the functionality and safety of these materials used for taste masking. Research should focus on how long the taste-masking effect lasts, and ensure that it does not interfere with taste perception for too long. Further investigation should be carried out to invoke guarantee that the taste masking technology or the material used for taste masking does not interfere with the efficacy or bioavailability of the active substance. Continued research and development in this area are necessary to improve the acceptability and effectiveness of medications, particularly for children.

Author contributions

Lohare Rahul Sanjay: writing – original draft and visualization. Makka Krupali Ashokbhai: writing – original draft and visualization. Shubham Ghatole: writing – original draft and visualization. Subhadeep Roy: investigation and review and editing. Kardile Punam Kashinath: investigation and review and editing. Santanu Kaity: conceptualization, writing – review and editing, and supervision.

Data availability

No primary research results, software or codes have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

No conflict of interest to declare.

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