Introduction

1. Introduction

The administration of medications to pediatric patients is in many ways difficult because health care providers and parents are faced with many challenges not experienced or experienced to a lesser degree, than when medications are provided for and taken by adults. Today many antimalarial drugs that are used for some pediatric patients are not in appropriate dosage forms for use by children (Nahata, 1999).

Further, majority of the orally administered drug substances are of very to extremely bitter taste. In most cases, the solid formulations are coated with advice not to chew but to swallow the intact tablet. However, for small children the administration of the dose of a whole tablet is frequently not recommended and to administer tablets in general is not recommended. Only liquid formulations should be given or if these are not available, the tablet should be crushed to a suspension and administered by a spoon. The bitter taste in such cases is frequently a serious problem.

Pediatric drug formulation development is one of the most difficult tasks. For pediatric formulation, the ideal drug formulation should be effective, well tolerated, stable, affordable, and have good palatability, i.e. acceptable taste, after-taste and smell (Table 1.1). Excellent palatability is a major factor in drug formulation compliance in the pediatric age group (Grob, 1992; Mattar, 1975). Moreover, a negative attitude by the parent for the use of drugs is easily transferred to the child (Mattar, 1975).

Table 1.1 Characteristics of an ideal drug for children

Effective
Acceptable safety record, researched and labeled for pediatric age group
Available in appropriate dosage and size, and suitable form
Stable (long shelf-life)
Acceptable palatability (taste, aftertaste, texture and smell)
Affordable
Easy storage and transportability

Various taste masking techniques such as the addition of sweeteners and flavors, coating with polymers, adsorption to ion-exchange resin, and chemical modifications such as the use of insoluble prodrugs have been reported. Each technique has its own disadvantages. Addition of sweeteners and flavors is not very successful for extremely bitter and water soluble drugs. Ion-exchange resins are functional group specific (amino group) and sometimes cause delayed drug release while coating with polymer requires sophisticated instruments. Chemical modification may alter the pharmacokinetic of drug substance.

In present vocation solid dispersions, cyclodextrin complexation and microparticles were prepared to study their comparative bitter taste masking efficiency. Since varying physicochemical properties of drugs affect the efficiency of systems, 3 different drugs artemether, mefloquine hydrochloride and primaquine phosphate, based on solubility characteristics, were exercised for study. All the 3 drugs are used in malaria. Taste masking of these drugs will help to improve the pharmacotherapy.

Solid dispersion is one of the promising methods to formulators due to its ease of preparation and reproducibility. Drug when dispersed in an inert carrier by melting, solution formation or solvent melting yields solid dispersion. Solid dispersion of drug with the help of polymers, sugar or other suitable agents, is very useful for taste masking.

Cyclodextrin is widely used in pharmaceutical industry for its various applications in dissolution improvement, stability improvement and drug safety improvement. Cyclodextrin is a sweet, non toxic, cyclic oligosaccharide obtained from starch. Cyclodextrin is capable of making the bitterness 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.

Microencapsulation using coacervation and crosslinking method are popular. These methods avoid use of special instrument, hazardous organic solvent and are easy to scale up. Further these microparticles may be incorporated into various pharmaceutical formulations including tablets and dry suspension without affecting bioavailability.

The taste masked drugs were developed in appropriate formulation.

The surest method to evaluate taste is sensory testing with human volunteers. However since the sensory test is difficult to perform each time, a simple alternative method is required. Hence mini-column, an *in vitro* model, was developed to evaluate the bitterness score of routine batches and thus avoiding the involvement of human volunteers in it.

Review of mechanism of taste transduction and techniques used for masking and evaluating bitterness

1.1. Introduction

The taste buds and olfactory receptors are well developed in children and the number of taste buds decreases with age. With globalization and increasing ethnic diversity, cultural and ethnic background should also be taken into account as well when one determines the favorable taste and flavor for a specific country or community.

Taste together with smell is collectively called chemical senses because chemical substances are adequate stimulants to elicit these sensations. Chemical senses are often referred to as the protopathic sensation, as opposed to the epicritic sensation such as vision and audition. All the sensations have two aspects: one is an affective aspect relating to pleasure and displeasure, acceptance and rejection, or preference and aversion; and the other is a cognitive aspect concerning discrimination of quality and intensity of stimulants. The term of protopathic sensation for chemical senses may be derived from notions that chemical senses are universally found in organisms ranging from bacteria to humans, and that the chemical senses involve affective feelings rather than analytical discrimination, especially when we intake complex edibles.

1.2. Mechanism of taste transduction

1.2.1. Basic taste and taste receptor cells

Sapid chemicals contained in food or beverages have first access to our gustatory system at taste receptor cells. The peripheral taste system is schematically illustrated in Fig. 1.1. The receptor cells are pear shaped and contained in a cluster of 50-100 neuroepithelial cells, which is called a taste bud. The taste bud is about 70 μm high and has a diameter of about 40 μm. A majority of taste buds are found on the dorsal surface of tongue in small elevations called papillae such as the fungiform, foliate and circumvallate papillae. Taste buds are also distributed in the oropharyngeal tissues including the soft palate, pharynx and epiglottis. They are innervated by afferent fibers belonging to three cranial nerves (facial nerve,

glossopharyngeal nerve and vagus nerve). The chorda tympani (CT), a branch of facial nerve, innervate taste buds in fungiform papillae on the anterior tongue. Other nerves innervate a different group of taste buds on the posterior tongue and the oral tissues.

Chemical stimulation induces receptor potentials in taste cells followed by impulse traffic in the taste nerve fibers. Neural activity in the taste nerve reflects electrical events occurring in the taste cells, e.g. the greater the amplitude of depolarization in taste cells, the more the number of impulses in taste nerve. Although a vast array of chemicals generate the receptor potential in taste cells and impulse discharges in nerve fibers, psychological and physiological evidence have shown that they are classified into few classes of taste quality (each class is also termed a basic taste): salty, sour, bitter and sweet.

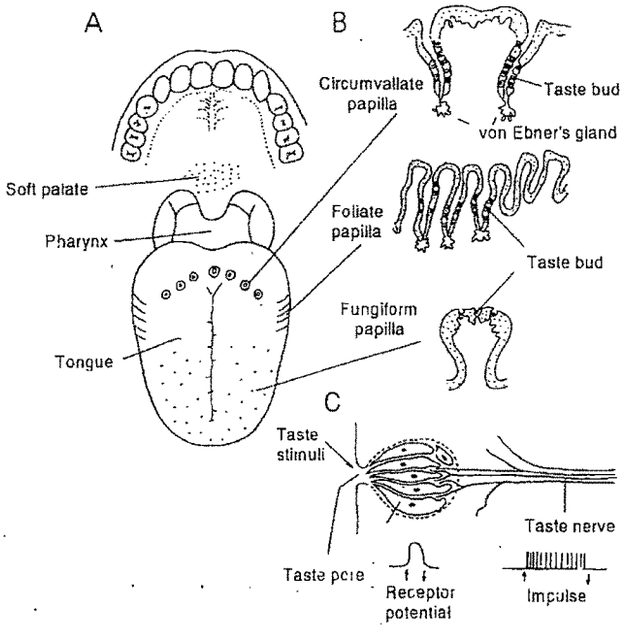

Figure 1.1 Schematic drawings of locations of the taste buds in the mouth (A), transverse sections of circumvallate, foliate and fungiform papillae (B) and a taste bud and taste nerve fibers with electrical events (C).

Examples of chemical inducing each basic taste in humans are respectively, NaCl, citric acid, quinine hydrochloride and sucrose. It is well documented

that each of the taste fibers responds most dominantly to one of the four taste stimuli. In addition to these four basic tastes, recent studies propose umami as a basic taste, the unique taste elicited by glutamate (Kawamura and Kare, 1987).

1.2.2. Taste transduction

Each basic taste seems to be transduced by different mechanisms in taste cells. However, transduction mechanism may be divided into two types, depending on whether chemical stimuli directly activate ion channels in the taste cell membrane or they bind to cell surface receptors coupled to intracellular signaling pathways. Some basic taste is transduced by either mechanism depending on species of chemical stimuli.

1.2.2.1. Salty and Sour

Inorganic salts such as NaCl and LiCl induce salty taste in humans. When the taste buds are stimulated by a solution of sodium salt, Na^+ ions flow into taste cells through ion channels in the apical membrane of the cells. The movement of these ions is dependent on the concentration of Na^+ ions. Positively charged Na^+ ions, when accumulated inside a taste cells, develop a depolarizing receptor potential, which leads to activation of voltage-dependent Ca^{2+} channels, an increase of intracellular Ca^{2+} and subsequent release of neurotransmitter to afferent nerve fiber (Fig 1.2a). The permeation of Na^+ ions is blocked by amiloride, a diuretic that blocks Na^+ entry through epithelial Na^+ channels (Garty and Benos, 1988). Therefore, ion channels permeable to Na^+ ions are thought to be amiloride-sensitive Na^+ channels.

Involvement of these channels in salty taste transduction was first demonstrated by measurement of trans-epithelial current through lingual epithelium and subsequently by a whole-cell clamp study of isolated taste receptor cells (Avenet and Lindemann, 1988; Heck et al., 1984). Amiloride-sensitive Na^+ channels also allow the flow of Li^+ ions in to taste cells, but not K^+ ions.

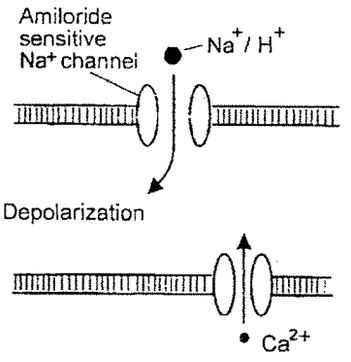

Figure 1.2 Transduction mechanism in taste buds. Na^+ and/or H^+ enter the taste cell through amiloride-sensitive channels. Positively charged ions induce depolarization of the cell. Voltage dependent Ca^{2+} channels are present on th ebasolateral cell membrane. On depolarization, activated Ca^{2+} channels allow the inflow of Ca^{2+}, leading to transmitter release.

The salty taste of LiCl may be explained by its sharing the channels with NaCl, but the taste of KCl that is perceived by humans as salty, although partially, is not explained by this. Although amiloride-sensitive Na^+ channels seems to play a major role for transducting sodium salt, amiloride–insensitive mechanisms also exists in some species of animals and a certain type of taste buds. In mudpuppies (*Necturus maculosus*), afferent neural responses induced by NaCl are not affected by the exposure of lingual epithelium to amiloride (McPheeters and Roper, 1985). In rats, where amiloride-sensitive Na^+ channels for taste transduction have been best described, the taste receptor cells in circumvallate papillae don't have amiloride sensitivity (Doolin and Gilbertson, 1996). Because of their smaller size, Na^+ ions permeate not only the apical taste cell membrane but also the tight junctions between taste receptor cells (the paracellular pathway) (Simon et al., 1993). Ionic flow through this pathway leads to an increase in the intercellular Na^+ concentration and affects ion channels on the baso-lateral membrane of taste cells (Mierson et al., 1996; Ye et al., 1991).

Amiloride-sensitive Na^+ channels in mammalian taste cells are also permeable to protons (H^+), which were dissociated from hydrochloric acids or citric acid, and thus are proposed to play a role in sour taste (Gilbertson et al., 1992). This may explain why amiloride suppresses the sourness of NaCl and LiCl

perceived in humans (Ossebaard and Smith, 1996). In mudpuppy taste cells, a different mechanism is proposed for sour taste transduction. Protons don't permeate the taste cell but block K^+ channels that are localized at the apical cell membrane (Kinnamon and Roper, 1988a) (Fig 1.2b).these channels are open at rest, whose blockage thereby leads to depolarization of taste cells. Similar blockage of apical ionic channels occurs in response to other tastants, such as quinine and $CaCl_2$, which taste bitter (Kinnamon and Roper, 1988b). However, the decrease of ionic currents is not very large compared to other inward currents (Na^+ and Ca^{2+}). Therefore apical K^+ channels seem to be only partially involved in generating receptor potential for bitter substances.

1.2.2.2. Bitter and Sweet

Sweet taste is induced by various saccharides or synthetic sweeteners such as sodium saccharin. These chemicals are relatively larger molecules. Bitter tasting compounds such as quinine and denatonium benzoate are also large, although small sized salts such as KCl, $MgCl_2$ and $CaCl_2$ are partially perceived as bitter in humans. For large sized molecules, transduction is more likely to be mediated by binding chemicals to membrane receptors in the cell membrane rather than by direct interaction of chemical with ionic channels. Such a suggestion comes from an early study, in which enzymatic treatment of the taste cell membrane caused specific loss of sweet taste (Hiji, 1975).

Bitter and sweet substances are though to bind to specific receptors coupled to guanine-nucleotide-binding proteins (GTP, G-proteins). Being activated by binding to GTP inside the taste cell membrane, G-proteins stimulate second-messenger systems in the cytoplasm. Recent molecular studies have shown that several G-proteins (G_q, G_i, G_s) are expressed in the tissue of taste buds, and among these, gustducin is found to be taste-cell-specific (McLaughlin et al., 1992). By eliminating the gene encoding the alpha-subunit of gustaducin (targeted gene replacement), Margolskee and others "knocked out" gustaducin in specially bread mice and examined their taste responses by behavioral test and taste nerve recordings (Wong et al., 1996), surprisingly, in those mice, sensitivity to both bitter and sweet substances diminished. The presence of alpha-gustaducin in mammalian taste cells was demonstrated immunocytochemically (Boughter et al., 1997).

To transfer sensory information to the CNS, gustatory afferents are excited by neurotransmitters released from the taste cells. A rise in intracellular free Ca^{2+} is crucial for inducing neurotransmitter release, which is in many cases linked to a depolarization of receptor cells (Roper, 1989). The concentration of Ca^{2+} in taste cells was first studied in dissociated taste cells from rat circumvallate papillae (Akabas et al., 1988).

A potently bitter tasting substance, denantonium, caused a rise of intracellular Ca^{2+}, suggesting that Ca^{2+} was released from an internal store by a mechanism independent of membrane depolarization. In mudpuppy, the rise of intracellular Ca^{2+} in taste cells was inhibited by an inhibitor of phospholipase C (Ogura et al., 1997). Denatonium increased outward currents, which hyperpolarized mudpuppy taste cells. The denatonium-induced outward current was blocked by GDP-beta-S, a blocker of G-protein activation.

Therefore, bitter substances seem to bind receptors (G-protein-coupled receptors) on the apical taste cell membrane and produce a second messenger, inositol 1, 4, 5 – triphosphate (IP_3), via activation of G-protein and phospholipase C (Fig 1.3a). The increase in intracellular IP_3 leads to release of Ca^{2+} from internal stores such as endoplasmic reticulum, because IP_3 receptors are present on the reticular surface close to the apical cell membrane (Hwang et al., 1990). However, this release is not induced in responses to quinine, more often used as bitter substance. Furthermore, quinine induces depolarization of taste cells (Ozeki, 1971). Therefore, transduction mechanisms other than an IP_3 pathway may also exist.

In earlier biochemical studies searching for sweet taste receptors, efforts were directed towards purification of specific proteins in the lingual epithelium that bind to sweet compounds (Dastoli and Price, 1966). Nowadays, the receptors are thought to be G-protein-coupled receptors. In the anterior tongue, taste epithelium of rats prepared for biochemical assay responds to sucrose with an enhancement of adenyl cyclase activity, and this activity depends on the presence of guanine nucleotides, suggesting the involvement of G-proteins (Striem et al., 1989).

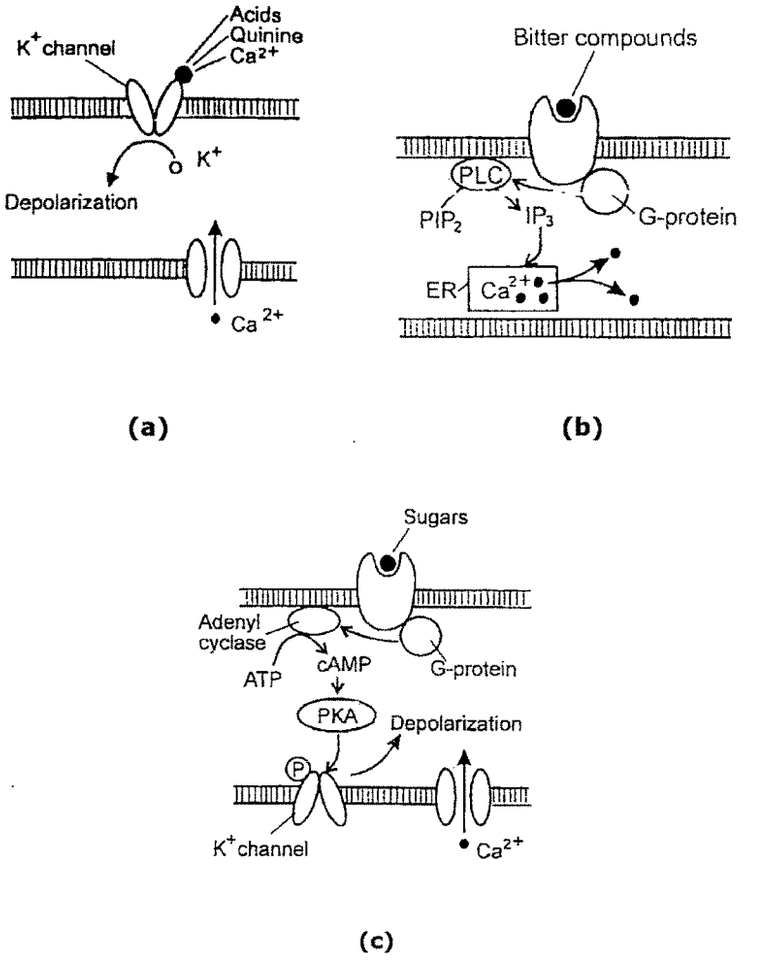

Figure 1.3 Transduction mechanism in taste buds. (a) – Acids, quinine and Ca^{2+} depolarize taste cells by closing K^+ channels. (b) – Bitter stimuli bind to G-protein-coupled receptors to activate phospholipase C (PLC), leading to release of Ca^{2+} from intracellular stores. (c) – Sugar binds to G-protein-coupled receptors to activate adenyl cyclase. Increased cAMP closes K^+ channels on the basolateral membrane, resulting in cell depolarization. PIP_2, phosphatidyl inositol 4,5-diphosphate; ER, endoplasmic reticulum; PKA, cyclic AMP-dependent protein kinase (protein kinase A); P, inorganic phosphate.

Sucrose increases the membrane resistance of mouse taste cells, and this increase is mimicked by cAMP injected into the cells (Tonosaki and Funakoshi, 1988). Whole cell recordings have shown that the increase of membrane resistance is induced by inactivation K^+ channels caused by cAMP-dependent

protein kinase (Avenet et al., 1988). These data strongly suggest that a transduction mechanism of sucrose involves specific receptors, a G-protein and cAMP, leading to depolarization of the taste cells (Fig 1.3b). on the other hand, synthetic sweeteners such as saccharin increased the cellular content of IP_3, but did not raise cAMP level (Bernhardt et al., 1996), suggesting that the sweeteners utilize different G-proteins from those used by sucrose to initiate the cascade for intracellular signaling. However, the sweeteners block the same K^+ channels as does cAMP in transducing the sucrose taste (Cummings et al., 1996).

1.2.2.3. Umami, taste of amino acids

Catfish have highly sensitive taste receptors that respond to low concentration (less than 10^{-8}M) of amino acids such as L-areginine, L-proline and L-alanine (Caprio et al., 1993). High affinity and specificity for these amino acids allowed biochemical isolation of receptors that bind to these taste stimuli. Membrane vesicles isolated from catfish taste buds have been incorporated into lipid bilayers on the tips of patch pipettes and stimulated by amino acids (Teeter et al., 1990).

L-arginine and L-proline activated non-selective cation channels in the bilayers, suggesting that these amino acids directly activate ion channels (Fig 1.4). In a subset of catfish taste cells, L-arginine elicited an increase in intracellular Ca^{2+}, which leads to neurotransmitter release in taste cells (Zviman et al., 1996). On the other hand, L-arginine didn't elicit a conductance change in the membrane patch. L-arginine seems to be transduced by pathways where second messengers cAMP and IP_3 are involved, rather than by direct activation of ion channels (Kalinoski et al., 1989).

In humans, L-glutamine is believed to impart a unique taste termed "umami", which constitutes a fifth basic taste (Kawamura and Kare, 1987). A receptor for this amino acid has been recently identified by molecular cloning (Chaudhari et al., 1996). A G-protein coupled metabotrophic receptor, mGluR4, is expressed in taste buds but not in surrounding non-taste epithelium.

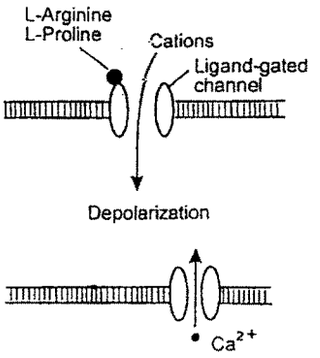

Figure 1.4 Transduction mechanism in taste buds. Some amino acids activate ligand-gated channels, causing the inflow of cations.

A behavioural assay shows that L-2-amino-4-phosphonobutyrate, a specific ligand for mGluR4, and monosodium glutamate induces similar taste in rats. Therefore, umami is most likely to be perceived by binding of monosodium glutamate to mGluR4.

1.3. 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 (Kleinert et al., 1993).

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; conventional granulation; use of ion-exchange resins; spray congealing with lipids; formation of inclusion complexes with cyclodextrins; freeze-drying process; making multiple emulsions; and use of gelatin, gelatinized starch,

liposomes, lecithins or lecithin-like substances, surfactants, salts, or polymeric membranes.

1.3.1. 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 (Sapone et al., 1992). 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 (Kondo and Nishimura, 1991).

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 (Ueki et al., 1993). 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 (Lankford and Becker, 1951).

Glycyrrhiza and xanthan gum are used to improve the taste of extract containing pogostemi herba (Okudaira and Kakuta, 1997). 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 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, H2-blockers, etc (Pandya et al., 1998).

Liposome-associated flavorents have been reported to mask the bitter taste of pharmaceuticals in aqueous suspensions (Popescu and Mertz, 1991). 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. Artificial sweeteners such as neohesperidine dihydrochalcone and hesperidine dihydrochalcone 4'-b-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 (Baer, 1990).

Low levels of mono ammonium glycyrrhyzinate 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. Neohesperidin dehydrochalcone was used in pharmaceutical formulation to mask the bitter taste (Cano et al., 2000).

A study to quantify the degree of suppression of the perceived bitterness of quinine was performed 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 (Shimizu et al., 2003).

Lactisole, a sweetness inhibitor, possesses great potential in the taste masking of pharmaceuticals (Kurtz and Fuller, 1993). 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 (Kobayashi et al., 1992). Table 1.2 summarizes taste masking of various drugs by flavors, sweeteners, and amino acids.

Table 1.2. Taste masking with flavors, sweeteners, and amino acids.

Sr. no.	Drugs	Type of formulations	Taste masking agents	References
1	Eucalyptus oil	Mouthwashes/ cough drops	Fenochrome, borneol or isoborneol	(Hussein and Bareclon, 1991)
2	Benzethonium chloride	Dentrifrices	Stevia-based sweeteners extract and glycerin	(Yokoo and Hirohata, 1993)
3	Zinc acetate dihydrate	Lozenges	Anethol-beta-cyclodextrin complex and saccharin	(Eby, 1992)
4	Aspirin	Medicated Floss	Sodium phenolate	(Fuisz, 1991)
5	Thymol	-	Anethole,	(Montenegro

			eucalyptol and methyl salicyalte	et al., 1997)
6	Ibuprofen	Syrup	Sodium citrate dehydrate, sodium saccharin and refined sugar	(Depalmo, 1993)
7	Theophylline	Solution	d- sorbitol, sodium saccharin, sodium glutamate and vanilla essence	(Maegaki et al., 1993)
8	Chloramphenіramine, pheylpropanolamine	-	Sodium bicarbonate, citric acid and orange/cream flavor	(Brideau, 1994)
9	Famotidine	-	Sodium bicarbonate, citric acid and lemon flavor	(Wehling and Schuehle, 1993a)
10	Acetaminophen	-	Sodium bicarbonate, citric acid and cherry flavor	(Wehling and Schuehle, 1993b)
11	Guaifenesin	-	Monosodium glycyrrhyzinate	(Fawzy et al., 1998)
12	Caffeine	-	Starch, lactose and mannitol	(Matsubara et al., 1990)
13	Antichlolesterolemic saponins	-	Glycine, alanine and flavors	(Watabe et al., 1992)
14	Vitamin B, sod-5'-ribonucleoside (inosinate)	Oral liquid	Orange and fruit flavor	(Kobayashi et al., 1992)
15	Ibuprofen	Syrup	Sodium citrate	(Depalmo,

			dehydrate, sodium saccharin	1993)
16	Diclofenac	-	Alkali metal carbonates and bicarbonates	(Reiner and Reiner, 1997)
17	Minerals such as potassium, calcium, magnesium, iron, copper, chromium, zinc, and mixtures	-	Tannic acid glycyrrhizin and acesulfame potassium	(Bakal and Snyder, 2000)
18	Leuprolide	Metered dose inhaler suspension	Aspartame and methol	(Zheng et al., 2001)

1.3.2. 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 (Mozada, 1987). The taste of cimetidine can be improved by granulating it with glyceryl Monostearate (Gottwald et al., 1991).

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 (Chau and Cherukuri, 1991). The taste of isoprothiolane can be masked by mixing it with hydrogenated oil at 80^0C and spray dried. The resulting granules are coated with hydroxypropyl methylcellulose (Masuda and Takahashi, 1986).

Acetaminophen granules are sprayed with molten stearyl stearate, mixed with suitable tablet excipients, and incorporated into a taste-masked, chewable tablet formulation (Gowan and Bruce, 1993). Bitterness-free syrup of carbetapentanecitrate, diphenhydramine HCl acetaminophen, and Noscapine HCl can be formulated using polyglycerine fatty acid ester, glycerin, and chained triglycerides (Miura et al., 1992).

1.3.3. 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 (Kinoshita and Shibuya, 1987). Homogenated suspensions of phosphatidic acid and b-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 (Kasturagi and Kurihara, 1993). Table 1.3 summarizes taste masking of various drugs with lipophilic vehicles.

Table 1.3. Taste masking with lipophilic vehicles

Sr. no.	Drugs	Technique/ formulation	Taste masking agents	References
1	Guaifenesin	Melt granulation	Carnuba wax and magnesium aluminum silicate	(Mozada, 1987)
2	Cimetidine	Granulation	Glyceryl Monostearate	(Gottwald et al., 1991)
3	Gabapentin	Coating	Gelatin and mixture of partially hydrogenated soybean oil and glyceryl Monostearate	(Chau and Cherukuri, 1991)
4	Isoprothiolane	Spray drying and coating	Hydrogenated oil and HPMC	(Masuda and Takahashi,

				1986)
5	Acetaminophen	Spraying/tablet	Molten stearyl stearate	(Gowan and Bruce, 1993)
6	Acetaminophen, diphenhydramine, carbetapentane citrate, and noscapine HCl	Syrup	Polyglycerine fatty acid ester, glycerin and chained triglycerides	(Miura et al., 1992)
7	Quinine, L-leucine, iso-leucine, caffeine, and papaverine	-	Homogenated suspension of phosphatidic acid and beta-lactoglobulin	(Kasturagi and Kurihara, 1993)
8	Talampicillin HCl	-	Magnesium aluminum silicate with soybean lecithin	(Block et al., 1990)
9	Clarithromycin	-	Glyceryl Monostearate and AMCE	(Yajima, 1997)
10	Indeloxazine HCl	Fluidized bed drying	Hydrogenated oil and surfactants	(Lunstroth et al., 1999; Sugao et al., 1998)

1.3.4. 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., microemulsion technology, has been used for taste masking of powders, chewable tablets, and liquid suspensions.

1.3.4.1. 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 (Block et al., 1990).

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 (Block et al., 1990). 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 (Shen, 1996).

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 (Ogasawara and Ueda, 1992). 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 (McCabe et al., 1992).

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 (Hayashida and Hatayama, 1993). Cross carmellose sodium has been used to mask the bitter tasting active agents and to impart rapid disintegrating properties to the tablet (Augello et al., 2000). 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 (Gergely et al., 1993).

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 (Morella and Lucas, 1992).

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 (Moroi et al., 1993). 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 (Tabata and Yoshimi, 1992a; b).

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 (Nakamura et al., 1991). 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 (Shirai, 1993). 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) (Shirai et al., 1996).

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/poly-sorbate 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 (Motola et al., 1995). The same drug can also be formulated, rotogranulated, and coated with a solution containing hydroxyethyl cellulose and hydroxypropyl methylcellulose in water. The taste-masked granules are compressed into chewable tablets (Roche and Reo, 1992).

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 (Wheatley and Erkoboni, 1992). 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 (Roche et al., 1993). 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 (Olthoff et al., 1988). 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 (Roche, 1991) or with cellulose acetate (39.8% acetylation); Eudragit E 100; and polyvinyl pyrollidone (Hoy and Roche, 1993). 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 over coated 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 (Mori et al., 1993).

The taste-masked microcapsules were developed 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. The microcapsule composition may be incorporated into any number of pharmaceutical formulations, including chewable tablets, effervescent tablets, powders, liquid dispersions, etc (Friend et al., 2000).

1.3.4.2. 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 (Meyer and Mazer, 1993). Tylenol Geltabs that use the gelatin-coating process offer ease of swallowing and taste masking. The notable disadvantage of this preparation is poor stability in hot and humid climates (Meyer and Mazer, 1997).

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 (Alexander et al., 1996). For mint-

flavored oral pharmaceutical gums, incorporating a prolamine/cellulose ingredient of high pH can reduce bitterness of flavor (Patel et al., 1993). 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 (Nanda et al., 2002).

Terfenadine mixed with sodium alginate, carrageenan, and macrogol-400 gives a taste-masked formulation (Andou et al., 1998a). Ibuprofen and sodium alginate mixed in water and added dropwise to an aqueous solution of calcium chloride gives a tasteless and odorless jelly (Andou et al., 1998b). 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 (Toraishi et al., 1988). 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 (Ozer and Hincal, 1990). 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 (Friend, 1992). The bitter taste of clarithromycin can also be masked by granulating it with carbopol followed by rotogranulation with polyvinyl pyrollidone (PVP) solution (Saleki and Keske, 1997).

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 (Sakakibara et al., 1993). 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 (Mapelli et al., 1991). The same drug can also be taste masked by mixing it with Eudragit RS-100 in methylene chloride followed by spray drying (Morella et al., 1997). Nizatidine

has improved taste when mixed with Eudragit E-100 in ethanol/water (80:20) and spray dried (Cumming and Harris, 1999). Melt granulation with water-soluble substances successfully reduces the bitterness of cetraxate and 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 (Haramiishi, 1993a; b).

Antibacterial quinolone carboxylic 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 (Lange et al., 1992). 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 (Michaelis et al., 1993).

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 (Sjoeqbist, 1993). 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 (Shen, 1991).

Bifemelane HCl has been formulated as "dry syrup" to reduce bitterness. The drug is kneaded, circulated, coated with glycerin mono-stearate, and over coated with Eudragit L30-D-55, polyethylene glycol, and talc. The mixture is then sprayed with sucrose to produce non bitter dry syrup (Nomura and Izumida, 1993). 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 (Nitta et al., 1992).

1.3.4.3. 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 (Ryu, 1991). Table 1.4 summarizes taste masking of drugs by polymer coating.

Table 1.4. Taste masking by polymer coating

Sr. no.	Drugs	Technique	Polymers used	References
1	Pinaverium bromide	Coating	Cellulose or shellac	(Block et al., 1990)
2	Propantheline bromide	Coating	L-HPC, EC	(Block et al., 1990)
3	Ibuprofen	Air-suspension coating	Methacrylic acid copolymer (Eudragit)	(Shen, 1996)
4	Triprolidine HCl	Dispersion coating	HPMC	(McCabe et al., 1992)
5	Dimenhydrinate	-	Eudragit or CMC or starch	(Gergely et al., 1993)
6	Cefeanel daloxate HCl	Granulation and coating	PVP, EC, HPM C, trisodium citrate	(Tabata and Yoshimi, 1992b)
7	Enoxacin	Granulation and coating	HPC, HPMC, EC	(Nakamura et al., 1991)
8	Sparfloxacin	Granulation and	L-HPC, EC,	(Shirai,

		coating	HMC/EC, HPMC, titanium dioxide and sucrose, fatty acid ester mixture	1993; Shirai et al., 1996)
9	Ibuprofen	Rotogranulation and coating	HEC, HPMC	(Roche and Reo, 1992)
10	Aspirin	-	Cellulose acetate latex and triacetin	(Wheatley and Erkoboni, 1992)
11	Famotidine	Rotogranulation and coating	HPC, HPMC, cellulose acetate	(Roche et al., 1993)
12	Amoxicillin trihydrate	Granulation	MCC, L-HPC	(Olthoff et al., 1988)
13	Acetaminophen	Coating	Cellulose acetate, cellulose acetate butyrate, HPC/Cellulose acetate, Eudragit E 100, PVP	(Hoy and Roche, 1993; Roche, 1991)
14	Morphine HCl	Coating	Cellulose, Eudragit NE 30D	(Mori et al., 1993)
15	Amiprilose HCl	Coating	Calcium gluconate and sodium alginate	(Nanda et al., 2002)
16	Terfenadine	Mixing	Sodium alginate, carrageenan, and macrogol – 400	(Andou et al., 1998a)
17	Beclamide	Microencapsulation	Gelatin	(Ozer and Hincal, 1990)
18	Clarithromycin	Rotogranulation	Carbopol, PVP	(Saleki and Keske, 1997)
19	Roxithromycin	Granulation and coating	PEG, Eudragit L 100-55	(Mapelli et al., 1991)
20	Nizatidine	Spray drying	Eudragit E 100	(Cumming and Harris, 1999)

21	Cetraxate HCl	Melt granulation and coating	Corn starch, macrogol-6000, Eudragit S-100	(Haramiishi, 1993a; b)
22	Ciprofloxacin	Microencapsulation	Eudragit NE 30D, HPC	(Michaelis et al., 1993)
23	Ibuprofen	Spray coating	Eudragit L 300, priopylene glycol, mannitol and flavor	(Shen, 1991)
24	Bifemelane HCl	Coating and spraying	Glycerin monostereate, Eudragit L 30-D-55, PEG, sucrose.	(Nomura and Izumida, 1993)
25	Cefuroxime axetil	Emulsion-solvent evaporation	Eudragit L-55 and RL	(Lorenzo-Lamosa et al., 1997)
26	Pirenzepine and Oxybutynin	Dispersion coating	Eudragit E-100, MCC, HPC	(Ishikawa et al., 1999)
27	Diclofenac	Microencapsulation	EC	(Al-Omran et al., 2002)
28	Nicorandil	Coating	Croscarmellose sodium, D-mannitol, and lactose	(Jin et al., 2001)
29	Levofloxacin	Coating	Eudragit E100, cellulose acetate	(Yu and Roche, 2003)
30	Cefuroxime axetil	-	Eudragit L-55 and RL	(Lorenzo-Lamosa et al., 1997)
31	Niflumic acid, ibuprofen	-	EC and HPMC	(Barra et al., 1999)
32	Peonjahwan	Coating	Eudragit	(Choi and Kim, 2000)
33	Diclofenac sodium	Microencapsulation	EC	(Al-Omran et al., 2002)
34	Ibuprofen	-	HEC and HPMC	(Li et al., 2002)

35	Trimebutine maleate	Microencapsulation	Polyvinylacetal diethylamino acetate (AEA)	(Hashimoto et al., 2002)
36	Aspirin	Coating	Shellac and HPMC	(Pearnchob et al., 2003)
37	Clarithromycin	-	Eudragit	(Tanigake et al., 2003)
38	Sildenafil citrate	Coating	HPMC, Eudragit NE30D and Eudragit E 100	(Itoh and Niwa, 2001)
39	Paroxetine	-	Eudragit L30D55, b CD, lecithin, Polacrilin K	(Meneaud et al., 2001)
40	Levofloxacin	Coating	Eudragit E100, CA	(Yu and Roche, 2003)
41	Eletripan, Ibuprofen, Pregabaline	Coated	EC	(Nouri et al., 2003)
42	Pirenzepine HCl Oxybutynin HCl	-	Eudragit E100, HPC	(Ishikawa et al., 1999)
43	Ondensetron HCl	-	Eudragit E100	(Khan et al., 2007)
44	Qunine sulphate	Coating	Eudragit E100	(Kayumba et al., 2007)
45	Roxithromycin	Microencapsulation	Eudragit S100	(Gao et al., 2006)

Note: HPMC – Hydroxypropyl methyl cellulose; HEC – Hydroxylethyl cellulose; HPC – Hydroxypropyl cellulose; L-HPC – Low substituted hydroxypropyl cellulose; CMC – Carboxy methyl cellulose; PVP – Polyvinyl pyrollidone; EC – ethyl cellulose; CA – Cellulose acetate; MCC – Microcrystalline cellulose; PEG – Polyethylene glycol.

1.3.5. 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. Vander Waals forces are mainly involved in inclusion complexes (Nanda et al., 2002).

There are only two theoretical possibilities:

1. the CD enwraps the bad tasting molecule (inclusion complex formation), impeding its interaction with the taste buds, or
2. the CD interacts with the gate-keeper proteins of the taste buds, paralyzing them.

The bitter taste of a substance disappears in the presence of beta-CD only, when the drug molecule which causes the bitter taste is complexed by an appropriate CD molecule. These complex molecules are strongly hydrated on their outer surface; therefore, they do not get attached to the taste bud receptors on the tongue in the mouth cavity (Szejtli and Szente, 2005).

Beta-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 (Kurasumi et al., 1991a).

Palatable ibuprofen solutions are prepared by forming a 1:11 to 1:15 inclusion complex with ibuprofen and hydroxypropyl b-cyclodextrin, respectively. The complex masked the bitter component but created a sore taste that was masked by sweeteners (Motola et al., 1991a). 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 beta-cyclodextrin. Besides masking its bitter taste, beta-cyclodextrin further enhances the blood sugar lowering effects of gymnemic acids (Ikezuki, 1990).

Formulation of mixtures of drugs and CDs without previous complex formation

The mechanism of the debittering process in these cases is the inclusion complexation of the bitter drug with the appropriate CD, because the bitter drug is also dissolved in the CD-saturated saliva. In the case of easily migrating (hydrophilic, well soluble, volatile/sublimable or of low melting point) drugs the complexation proceeds already in the dry (but not anhydrous!) powder mixture assuming that the CD contains the usual crystal water (in the case of beta-CD this is approximately 13–14 wt%).

In solid state the CD molecules located in the surface layer of the CD crystals will exchange their inclusion water molecules with the 'easily migrating' potential guest molecules, releasing the water molecules. Because the crystal lattice parameters of the formed complex are generally different from the ones of the water/CD complex, the surface layer will be 'peeled off' from the CD crystal, forming a new microcrystalline phase. The naked new CD crystal surface will repeat this process and depending on the particle size, temperature, humidity and degree of homogenity of the mixture. Within days or months all guest molecules will be included assuming that enough (or better an excess) CD is present in the mixture.

This process already begins during the powder mixing and continues during pelleting/granulation (particularly when water is present), accelerates during extrusion and tablet compression and continues during storage. The complexation process will be completed during dissolution of drug and CD in water, saliva, gastric juice, etc. Bitter drugs which do not form CD-complexes cannot be debittered with CDs! Table 1.6 summarizes taste masking of drugs by complexing agents.

Table 1.5. Taste masking of drugs by complexing agents

Drug	**CD**	**Reference**
Dextromethorphan HBr	Beta- and gamma-CD	(Szejtli and Szente, 2005)
Libexin HCl	Beta-CD	(Weiszfeiler and Szejtli, 1988)
Femoxitine HCl	Beta-CD	(Andersen et al., 1984)
Clofibrate	Beta- and gamma-CD	(Uekama et al., 1983)

Tetrachloroethylene	Beta-CD	(Suzuki and Ikura, 1975)
Tiaramide	Alpha-, beta- and gamma-CD	(Seiyaku, 1981)
Ibuprofen	Beta-CD, HP-beta-CD	(Grattan, 1993; Hunter and Yau, 1989; Motola et al., 1991b)
Alclofenac	Beta-CD	(Mitsubishi Yuka Yakuhin, 1981)
Ursodeoxycholic acid	Beta-CD	(Nakazawa et al., 1988; Widauer, 1995)
Chlorhexidine	Beta-CD	(Oi and Rytting, 1989)
Fenbufen	Beta-CD	(Miyaji et al., 1992)
Banexate	Beta-CD	(Suzuki et al., 1993)
Benzethonium chloride	Beta-CD	(Shimada et al., 1995)
Carbetapentane citrate	Beta-CD	(Kurasumi et al., 1991b)
Metronidazole benzonate	Gamma-CD	(Giordano et al., 1992)
Hexitidine	HP-beta-CD	(Gallopo, 1989; Schmidt and Kaupp, 1993)

1.3.6. 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 resonate through weak ionic bonding so that dissociation of the drug-resin complex does not occur under the salivary pH conditions. This suitably masks the unpleasant taste and 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.

Ion exchange resins can be classified into four major groups:

1. Strong acid cation-exchange resin.
2. Weak acid cation-exchange resin.
3. Strong base anion-exchange resin.
4. Weak base anion-exchange resin.

Strong acid cation resins (sulfonated styrenedivinylbezene 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 (Nanda et al., 2002).

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 (Manek and Kamat, 1981). Amberlite IRP-69, a cation-anion exchange resin, is used to mask the bitter taste of buflomedil (Honeysett et al., 1992). Oral liquid products of quinolones (orbifloxacin) and/or their derivatives are formulated using ion exchange resins, such as methacrylic acid polymer cross-linked 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 anti-caking agent (colloidal silicone dioxide) and a preservative (sorbic acid) (Gao et al., 2003).

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 (Lu et al., 1991). Table 1.6 summarizes taste masking of drugs using ion-exchange resins.

Table 1.6. Taste masking of drugs using ion exchange resins.

Sr. no.	Drug	Resin/complexing agent	Ref.
1	Chlorpheniramine maleate	Indion CRP 244, Indion CRP 254	(Manek and Kamat, 1981)
2	Diphenhydramine HCl	Indion CRP 244, Indion CRP 254	(Manek and Kamat, 1981)
3	Buflomedil	Amberlite IRP 69	(Honeysett et al., 1992)
4	ORBIFLOXACIN	Amberlite IRP 69	(Gao et al., 2003)
5	Chloroquine phosphate	Indion 234	(Agarwal et al., 2000)

1.3.7. Miscellaneous Taste-Masking Approaches

1.3.7.1. 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 (Niazi and Shemesh, 1987).

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 (Pather et al., 2002).

1.3.7.2. Rheological Modifications

Increasing the viscosity with rheological modifiers such as gums or carbohydrates can lower the diffusion 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 (Blase and Shah, 1993). 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 (Suzuki and Kawasaki, 1991). Gelatin and flavoring materials (chocolate flavor) mask the bitter taste of tannic acid by viscosity effects, when made into a jelly by cooling (Aoi and Murata, 1992). 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 (Kikuta et al., 1992).

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 (Skrabanga and Tully, 2000). Other commercially available pharmaceutical compounds delivered using the present approach are pseudoephedrine HCl, dextromethorphan, and ibuprofen (Popli and Zenaida, 1996).

1.3.7.3. Salt Preparation

Adding alkaline metal bicarbonate such as sodium bicarbonate masks the unpleasant taste of water-soluble ibuprofen salts in aqueous solution (Gregory et al., 1990). 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 (Nishikawa and Hayashi, 1992). Magnesium aspirin tablets are rendered tasteless by preparing magnesium salts of aspirin (Nanda et al., 2002). Penicillin prepared as N,N'-dibenzylethylene-diamine diacetate salts or N,N'-bis (deyhdroabiety)

ethylenediamine salts is tasteless (Nanda et al., 2002). Bitterness-reduced antitussive and expectorant compositions (tablets) of dihydrocodeine phosphate, DL-methylephedrine HCl, and D-chlorpheniramine maleate contain magnesium salts, sweeteners, starch, and cellulose (Nishikawa and Hayashi, 1993).

1.3.7.4. 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 (Damini and Tsau, 1987).

1.3.7.5. Group Alteration and Prodrug Approach

The alkyloxyalkyl carbonates of the clarithromycin 2′ position have remarkably alleviated bitterness and improved bioavailability when administered orally (Asaka et al., 1992). 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 (Hussain et al., 1988). A series of qualitative and empirical rules was collected by Sinkula. These may provide clues for improving the taste quality of objectionable tasting drugs (Sinkula, 1977). Table 1.7 summarizes qualitative structure-taste relationship.

Table 1.7 Empirical and qualitative structure-taste relationship

1	Compounds containing several hydroxyl groups are usually sweet (glycols, sugars and other carbohydrates).

2	An increase in molecular weight i.e. extending a homologous series, often changes from sweet to bitter. Further increase in homologation reduces drug solubility below taste threshold values.
3	Nitro groups present in a molecule are usa\ually indicative of bitter taste (chloramphenicol, picric acid).
4	Alkylation of a hydroxyl soup (etherification) destroys sweet taste.
5	Alkylation of an amine or amide usually produces a sweet tasting substance.
6	Alkylation of imide eliminates sweet taste N-alkyl saccharins are tasteless.
7	Addition of a phenyl group to a drug molecule causes or increases bitter taste and may be due to enhanced lipophilicity and/or preferential binding with bitter taste receptors.
8	An increase in chain branching decreases sweet taste and increases bitter taste.
9	Esterification enhances sweeteners e.g. ethyl butyrate, aspartyl dipeptide esters.
10	Introduction of unsaturation into a molecule increases bitter taste and pungency.
11	Primary amines enhance sweet taste especially if in close proximity to an electronegative group (-COOH), i.e. in certain D- and L-amino acids.
12	Secondary, tertiary amines and quaternary ammonium salts are bitter especially alkaloids, antibiotics and quaternary ammonium drugs.
13	Monosubstituted ureas are usually sweet although some are tasteless. Urea itself is bitter. Symmetrical molecules are often bitter.
14	Alphatic polyhalogenated compound are sweet (chloroform, 1,2-

	dichloromethane, dichloromethane).
15	Aromatic halogen substitution increases bitterness and is a function of the atomic weight of the halogen (for example, halogenated saccharins).
16	The presence of sulfur in an aliphatic molecule is usually associated with bitterness (-SH, -S-, -S-S-, C=S).
17	Sulfonic acids are usually bitter or tart.
18	Aldhydes are sweet. Aldehydo-semicarbazones are not as sweet as the parent aldehydes. Aldehyophenylhydrazones are not sweet.
19	Oximes are usually sweet or tasteless.

1.3.7.6. 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. (2003).

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 (Rathbone et al., 2003).

1.3.7.7. 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 microcapsules prepared were bio-equivalent to the commercial Enoxacin 100 mg tablets in beagle dogs (Ueda et al., 1993). 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 (Appelgren and Eskilson, 1990).

1.3.8. Approaches and Development other than Conventional Dosage Form

Zyck et al. 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 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 (Zyck et al., 2003).

1.4. Methods for evaluation of the bitterness

When pharmaceutical compositions comprised of ingredients with an unpleasant taste are formulated, it is important not only to mask the taste by pharmaceutical technology but also to evaluate the degree of improvement in

taste. Various reported methods for evaluation of bitterness are gustatory sensation test, mini-column method, E-tongue, inversion, shaking and paddle method (Yajima et al., 2002).

1.4.1. Gustatory sensation test

A taste panel, comprising specially trained humans, provides the most reliable characterization of taste properties. the taste panel comprises twenty human volunteers. One gm of drug was dispersed in 25 ml of water for 30 sec. Immediately after preparation, each volunteer held about 1 mL of the dispersion in mouth for 30 sec. After expectoration, bitterness was evaluated. The degree of bitterness was classified in 8 grades, corresponding to increasing bitterness, and a comparison of bitterness among samples was performed based on the total number of persons who selected 'bitter' and slightly bitter. The ranking scheme used is shown in Table 1.8. The threshold of bitterness was determined as the point at which half of the volunteers described the taste as bitter or slightly bitter (Yajima et al., 2002).

Table 1.8. Grading for gustatory sensory test

	Score
Tasteless	0
Very slightly bitter	0.5
Slightly bitter	1.0
Slight to moderate bitter	1.5
Moderately bitter	2.0
Moderate to strong bitter	2.5
Strongly bitter	3.0
Very strongly bitter	3.0 +

1.4.2. Paddle method

Paddle test with the accurately weighed drug sample was performed at 100 rpm according to method 2 under dissolution testing in the Japan Pharmacopoeia, using 900 mL using phosphate buffer solution, pH 6.5. Test solutions of 6.5 were used to clarify the relationship between the amount of drug release and bitterness at salivary pH (Yajima et al., 2002).

1.4.3. Mini-column method

The mini-column method is schematically shown in Figure 1.5. Columns with an inner diameter of 0.76 and with a length of 5 cm were used. Accurately weighed drug was packed in the column. After tapping the column 30, 10, or 3 times, absorbent cotton was packed on the sample bed to eliminate sample motion.

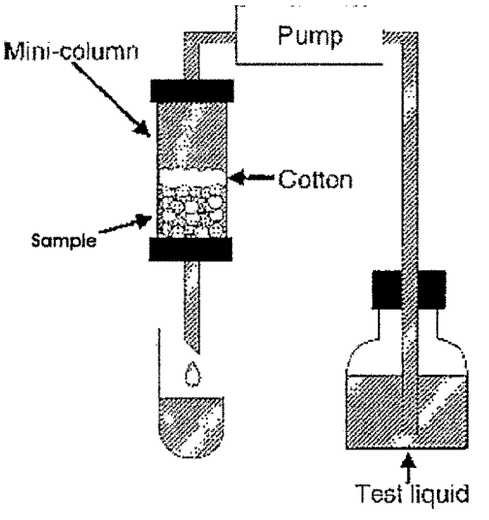

Figure 1.5. Mini-column Apparatus for Evaluating the Bitterness

The column was installed so that the filled drug sample was located in the bottom. Phosphate buffer solution, pH 6.5, filled the entire space of the column, and the nipple was then immediately attached to the top of the column. The upper part of the column was connected to a pump and filled with buffer solution in advance. The same solution flowed through this column. The eluate was collected at 2-min intervals for 6 min. Each eluate was used as sample solution and analyzed using appropriate analytical method (Yajima et al., 2002).

1.4.4. E-tongue

An electronic tasting apparatus such as the E-tongue (Alpha M.O.S., Toulouse, France) offers one solution to these challenges. This technique compresses timelines and lets researchers gather taste and dissolution data

simultaneously. Telescoping these steps reduces development time, development costs, subjectivity, bias, and safety concerns.

The e-tongue mirrors the three levels of biological taste recognition: the receptor level (taste buds in humans, probe membranes in the e-tongue); the circuit level (neural transmission in humans, transducer in the e-tongue) and the perceptual level (cognition in the thalamus in humans, computer and statistical analysis in the e-tongue). Applying principal component analysis (PCA) analysis to taste optimization studies can yield relevant information, allowing selection of an appropriate system to achieve a product with a desired taste profile (Kayumba et al., 2007; Legin et al., 2004; Murray et al., 2004; Zheng and Keeney, 2006).

Limitations of E-tongue:

- The software tools with an advanced chemometric software package for data measurement and analysis of results is required.
- The sensors have to be specifically formulated using specifically designed liquid sensors to correlate to various taste attributes.
- Need to develop flavor database based on training sets.

1.4.5. Inversion method

Accurately weighed amount of drug was packed in a syringe. Distilled water added to syringe which was inverted and returned to the upright position. 10 times at 3 sec intervals. Then the suspension was filtered through a membrane filter and the filtrate was used as the sample solution. The amount of drug release was estimated using appropriate analytical method. This method did not exhibit repeatability to poorly water soluble drugs, probably due to the hydrophobicity. Furthermore, it is impossible to filter the drug solution using a membrane filter, because of the liberated and particulate clogge the pores (Yajima et al., 2002).

1.4.6. Shaking method

Accurately weighed amount of drug was placed in 50 mL of centrifugation tube. Twenty milliliters of phosphate buffer solution, pH 6.5, was added to the

centrifugation tube. Then the centrifugation tube was shaken at 150 times per minute. After shaking for 10 or 30 min, the suspension was immediately centrifuged at 3000 rpm for 1 min. the supernatant was filtered through a membrane filter and this solution was analyzed using appropriate analytical method (Yajima et al., 2002).

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2. Objectives of the Work

Solid dispersions, cyclodextrin complexation and microparticles were designed and developed to mask the bitterness of drugs. For the study purpose three antimalarial drugs namely, artemether, mefloquine hydrochloride and primaquine phosphate were selected, based on their solubility characteristics. Similarly, five excipients namely, sodium saccharine, mono ammonium glycyrrhyzinate pentahydrate, beta-cyclodextrin (CD), Eudragit E (EE), and chitosan were selected for the study. It was hypothesized that the grafting of Eudragit E with CD may give better results compared to EE and CD. Hence Eudragit E-Beta-Cyclodextrin (EE-CD) was also evaluated for its bitter taste masking property.

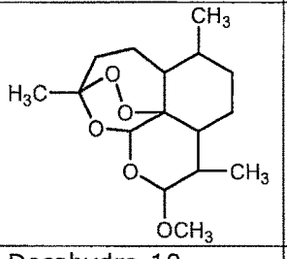
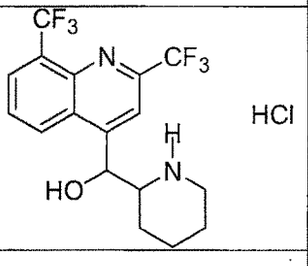
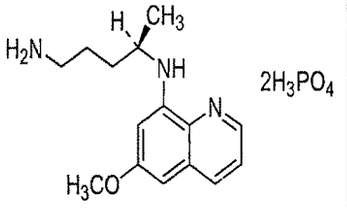
So the prime objectives in carrying out the work were,

1. To improve effectiveness of the therapy.
2. To improve patient and prescription compliance especially in pediatrics and geriatrics.
3. To enhance palatability of bitter antimalarial drugs and formulations.
4. To augment palatability without hindering drug release.
5. Development and validation of analytical methods for each selected antimalarial drug.
6. Screening and optimization of different techniques to improve bitterness of antimalarial drugs.
7. Development and validation of *in vitro* model to evaluate bitter taste of the drugs.
8. Development and evaluation of palatable dosage forms of antimalarials especially for pediatric and geriatric patients.
9. To carry out stability studies of the developed palatable dosage forms.

3. Drug Profiles

In the present work 3 drugs namely artemether, mefloquine hydrochloride and primaquine phosphate of antimalarial category were used. Table 1.8 gives physicochemical characteristics for artemether, mefloquine hydrochloride and primaquine phosphate.

Table 1.9 Detailed drug profiles.

	Artemether	**Mefloquine hydrochloride**	**Primaquine phosphate**
Official Status	International Pharmacopoeia - 2005	British Pharmacopoeia 2007	British Pharmacopoeia 2007
Structure			
IUPAC name	Decahydro-10-methoxy-3,6,9-trimethyl -3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin	(+) erythro-alpha-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol	N^4-(6-methoxyquinolin-8-yl)pentane-1,4-diamine bisphosphate
Mol. formula	$C_{16}H_{26}O_5$	$C_{17}H_{17}ClF_6N_2O$	$C_{15}H_{21}N_3O$, $2H_3PO_4$
Mol. Wt.	298.4	414.8	455.3
MP	86-90 ^{0}C	260 ^{0}C with decomposition	200 ^{0}C with decomposition
Solubility	Practically insoluble in water, very soluble in dichloro-methane and acetone, soluble in ethyl acetate and dehydrated ethanol	Very slightly soluble in water, freely soluble in methanol, soluble in alcohol	Soluble in water, practically insoluble in alcohol
UV maxima (nm)	----	222, 284 and 317 in methanol	206, 259 and 351 nm in distilled water