TASTE MASKING OF PEDIATRIC FORMULATION: A REVIEW ON TECHNOLOGIES, RECENT TRENDS AND REGULATORY ASPECTS

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ABSTRACT
Palatability of paediatric formulation is of greater importance when it comes to bitter active ingredients. So many advancements have taken place in the field of taste masking. Along with this the need to achieve global regulatory acceptability of such formulation is on rise. This creates a situation where more children are in safe and effective medications. Main objective of this review article is to give a view on various taste masking technologies employed in pharmaceutical field, their recent trends and pharmaceutical regulations.

Keywords: Taste, Taste masking, Technologies, Recent trends, Regulatory aspects.

INTRODUCTION
Most active pharmaceutical ingredients (APIs) are highly bitter and this is the main difficulty behind the palatable preparation for paediatric therapy. Adult formulations can be easily taste masked by coating the tablet or by putting the drug in capsule dosage form, techniques which are not suitable for paediatric groups. For this three broad approaches has been used, this include to create a barrier between taste receptors and drug (physical coating, encapsulation); to make chemical or solubility modifications (controlling pH, esters of drug); and to overcome the unpleasant taste by adding flavours and sweeteners.

Taste Vs flavours
The five primary tastes are sweet, umami, sour, salt and bitter. Sweet chiefly at the tip, salt on the dorsum anteriorly, sour at the sides, and bitter at the back of the tongue[4]. Sweet and umami have one receptor, whereas bitter has about 25 receptors—called T2Rs.

Taste receptors are located in gustatory (oral) and non gustatory tissues, including the gut, brain, human airway smooth muscles, and reproductive tissues.

Most of flavours and odours are perceived retronasally. Odors (chemicals) can reach the olfactory epithelium via the nose (orthonasal route) or mouth (retronasal route) and information is then sent to glomeruli in the olfactory bulb to mitral cells traveling to higher centers in the brain.

Person-to-person differences in the taste response to bitter chemicals are largely determined by genetic variation in a bitter receptor gene known as the TAS2R38 gene. Various studies showed that the phenotype-genotype relationship was modified by age. Genetic variation in bitter sensitivity may account for differences in medication compliance among children.

In conclusion, “bad taste” is going to be an ongoing pediatric drug formulation problem because of the diverse number of receptors, the multiple transduction pathways, and age-related sensitivity based on genotype. Infants and children live in different sensory worlds, and there is a need for validation of taste assessment methods[3].

By addressing the taste factor early in the product development can make pharmaceutical company save much. In so doing, they can get their medications to market more quickly, ensure patient compliance, gain market leadership and reap generous economic rewards. They can also stay in compliance with FDA’s final rule, which went into effect December 2000[5].

Taste masking
Using suitable agents one can reduce the unpleasant taste of bitter actives. But universally acceptable taste masking technology does not seem to exist. Whereas aversion to bitter taste is universal. Many current taste masking efforts are directed at reducing the negative attributes of paediatric dosage forms, which is a big challenge [2].

Finding a suitable taste masking method can impact the quality of taste masking and process effectiveness. There are many techniques developed for taste masking of bitter actives. These are as follows [6]:
- Addition of flavouring and sweetening agents.
- Complexation with ion-exchange.
- Microencapsulation.
- Prodrug approach.
- Inclusion complexation.
- Granulation.
- Multiple emulsion technique
- Gel formation.
- Bitterness inhibitor.
- Miscellaneous.

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

Three main approaches have been described below.

1. Sweetening and flavouring of paediatric formulation

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

Sweeteners

Different grades of sweeteners are available in order to control the taste. The following table 1 gives a compilation of most common artificial and natural sweeteners with their relative sweetness to sucrose and comments pertaining to each.
Artificial sweeteners like neohesperidin dehydrochloride, which is a bitterness suppressor and flavor modifier elicits a very intense sweet taste. It is obtained by hydrogenation of bitter flavones neohesperidin.

Recent Trends

Recently combination of high intensity sweeteners (sodium saccharin) with other sweeteners like mono ammonium glycyrrhizinate (Magna sweet available from Mafo of Camden, New Jersey) can provide specific sweetness profile with extended sweetness till the product being experienced in the mouth. The actives that had to be masked were Dextromethorphan HBr, guaifenesin, and pseudoephedrine HCI, all of which are bitter and tend to have a lingering unpleasant taste. To compete with the bitter receptors neuron firings, sodium citrate, an acid salt, was added causing competition within the receptors.

Another wise use of sweetener was done in the formulation of Calcium Atovastatin which is a highly bitter active. To prepare a patient compliant formulation, a great deal of work was done using sodium chloride to reduce the overall perception of bitterness. An extended sweetness profile was developed using Sucralose for initial sweetness burst and MagnaSweet for extended sweetness. A citrus mint flavour with menthol was chosen because the cooling effects of the menthol served to distract the organoleptic effects of the bitter taste. Cremophor was added to coat the receptors [8].

Regulatory aspects

While formulating paediatric formulation it has to be kept in mind that neonates and infants differs considerably from that of adults. They have differences in the metabolism and elimination of any ingredient with that of an adult[9]. Several regulatory bodies like EmeA (European Medicines Agency) have made guidelines pertaining to their use. Additional information can be found in documents published by European commission[10][11] and US Food and Drug Administration (US FDA). Some regulatory information’s made on some sweeteners have been given below.

Sucrose

Sucrose is the most commonly used sweetening agent. It is a disaccharide that is readily hydrolyzed in the intestine to the absorbable mono-saccharides fructose and glucose. It should be avoided for pediatric patients suffering from hereditary fructose intolerance. Formulations with high amounts of sugar should be avoided in therapy of paediatric patients, suffering from diabetes[12]. For preparations intended for long-term therapy large amounts of sucrose should be replaced by sugar-free formulations, since sucrose causes a decrease in dental plaque pH, dissolving tooth enamel and promoting dental caries.

Fructose

Fructose causes an elevation in blood glucose concentration and should therefore be avoided in patients suffering from diabetes. It is also contraindicated in patients with hypoglycemia or hereditary fructose intolerance [13]. It may cause laxative effects when administered orally at high doses.

Sorbitol, Xylitol

Sorbitol, and xylitol are mono-saccharides and are not readily absorbed from the gut and therefore are considered safe for diabetes patients. Sorbitol and xylitol may cause osmotic diarrhea[14]. Since sorbitol is metabolised to fructose, it is contraindicated in paediatric patients with hereditary fructose intolerance and hypoglycaemia – in severe cases it may cause damage of the liver accompanied with coma resulting in death in those patients. Especially intravenous administration of sorbitol should be avoided.[15]

Aspartame

Aspartame, a dipeptide of aspartic acid and a methyl ester of phenylalanine, is 150-200 times as sweet as sucrose. The phenylalanine component may be harmful in patients with phenylketonuria and contra-indicated in homoygous autosomal recessive patients [14]. Rare hypersensitivity reactions have been reported. Cross-reactivity with sulfonamides can occur.

Flavouring Agents

Flavour is a complex effect of three components taste, odor and feeling factors [16]. Suitable flavours are selected through taste panel studies. Most time blends of flavours were used to taste mask. Now since many flavours are odorous, the brain receives some additional impulses from the olfactory receptors in the nose which coordinate with the gustatory stimuli to produce the mingled sensation that is recognized as the flavour of a substance [17].

Flavouring agents may be classified as natural and synthetic [18]. Various natural flavours like Anise oil, Cardamom, wild cherry, lemon, Orange and peppermint are available [16]. Various flavors are mentioned in table 2.

Taste masking by flavours

Natural and artificial flavours can generally be described to have taste masking effect. Table 3 gives the list of taste maskers with basic complementing taste.

Table 3: Shows agents for masking and complementing the basic taste

<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural</td>
<td>Peppermint</td>
<td>Less stable</td>
</tr>
<tr>
<td>Artifical</td>
<td>Vanilla</td>
<td>Highly Stable</td>
</tr>
<tr>
<td>Natural and artificial</td>
<td>Strawberry</td>
<td>Effective at low concentrations</td>
</tr>
</tbody>
</table>

Syrups of cinnamon, orange, citric acid, cherry, cocoa, wild cherry, raspberry, or glycyrrhizin elixir can be used to effectively mask salty and bitter tastes in a number of drug products[19]. The cooling effect of some flavours aids in reducing after-taste perception. Eucalyptus oil is a major constituent of many mouth washes and cough syrup formulations. Menthol, chloroform and various salts are used as flavour adjuncts. They impart flavour and odour of their own to product and have a mild anaesthetic effect on sensory receptor organs associated with taste [21]. Vitamins containing oral solutions are rendered bitterness free by adding sugars, amino acids and apple flavours. Oral composition containing vitamin B-complex, sodium S-ribonucloleotide (inosinate), citrus (orange) flavors or fruit flavors also have remarkably improved taste[69].

Flavour enhancers and potentiator

Sugars, carboxylic acid (citric, malic and tartaric acid), common salt (NaCl), amino acids, some amino acid derivatives (eg. Mono sodium glutamate – MSG) are often employed.
Potentiators increase the perception of the taste of sweeteners and mask the unpleasant taste. Various potentiators include thaumatin; neohesperidine dihydro chalcone (NHDC) and glycyrrhizin increase the perception of sodium or calcium saccharinates, saccharin, acesulfame, cyclamates etc. Thaumatin along with sugar alcohols are used to achieve taste masking of bromhexine [6, 41]. Various taste suppressants and potentiators are given in table 4.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Taste suppressant and / potentiator used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromhexine</td>
<td>Mucoytic</td>
<td>Thaumatin and sugar</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Diuretic</td>
<td>Hydroxyflavones</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Diuretic</td>
<td>Gamma-amino butyric acid</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Antipyretic</td>
<td>Potentiators: Glycyrrhizin, Thaumatin and neohesperidine dihydrochalcone (NHDC)</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Anti diabetic</td>
<td>Sweeteners: Saccharin salts, acesulfame etc.</td>
</tr>
<tr>
<td>Sugar alcohol</td>
<td>Nutritive agent</td>
<td>Aldehydes (citral dimethyl acetal) and flavours</td>
</tr>
</tbody>
</table>

Examples of various classes of drugs of which the taste masking is achieved by the use of sweeteners and flavouring agents are listed in table 5 [25]-[40].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Dosage form</th>
<th>Taste</th>
<th>Taste masking agent used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eucalyptus oil</td>
<td>Freshener</td>
<td>Mouth wash</td>
<td>Bitter</td>
<td>Fenchone, Bomeol</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>NSAID</td>
<td>Syrup, suspension</td>
<td>Bitter</td>
<td>Saccharin sodium, Sucrose, sorbitol</td>
</tr>
<tr>
<td>Thymol, triclosan</td>
<td>Dental caries</td>
<td>Oral rinses</td>
<td>Bitter</td>
<td>Citrus flavour, Limonene</td>
</tr>
<tr>
<td>Zinc acetate dehydrate</td>
<td>Zinc supplement</td>
<td>Lozenges</td>
<td>Bitter</td>
<td>Saccharin sodium</td>
</tr>
<tr>
<td>Acetaminophene, Guaiifenesin and Dextromethorphan hydrobromide</td>
<td>Diet supplement</td>
<td></td>
<td>Suclarose</td>
<td>Aspartame, Saccharin sodium, Liquorice extract</td>
</tr>
<tr>
<td>Amino acids and proteins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydrocodeine phosphate, potassium guaiacol sulfate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Flurquine none</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin/Acetaminophen</td>
<td>NSAID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron compounds</td>
<td>Iron supplement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mineral supplement</td>
<td>Diet supplement</td>
<td></td>
<td>Glycyrrhizin, Acesulfame potassium</td>
<td>Caramel</td>
</tr>
<tr>
<td>Vegetable crude drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamins</td>
<td>Diet supplement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>Sympathomimetic drug</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Recent trends

Masking of astringent taste of zinc in mouth washes like Listerine mouth wash was done with a combination of sweet note [Vanillin – ethyl vanillin], one fruity note (raspberry and lemon), one spicy note (ginger, clove, anise cinnamon or mixtures) and in combination with taste receptor blocker, which eliminated the burning sensation and astringency associated with eucalyptol and zinc [22]. Coating agents like hydrogenated castor oil, Cremophor RH 40 identified as perfect coating agent for the receptor, because it masked the burns and produced end product [23]. Table 5 gives some examples to taste masking achieved with the help of sweeteners and flavourings.

Regulatory aspect

Anise oil: Used at a concentration up to 3000ppm in liquid preparations.
Cardomon: Used at 5-50 ppm
Wild cherry: Used at 50-800 ppm
Lemon: Used at 1000-10,000 ppm
Orange: Used at 500 ppm
Peppermint: Used at 8000 ppm in liquid formulation [16]
All the synthetic flavours used must be mentioned under Generally recognised as Safe (GRAS).


Complexation with Ion-exchange resins

Synthetic organic polymers comprising a hydrocarbon cross linked network to which ionisable groups are attached have the ability to exchange ions attracted to their ionized groups with ions of the same charge present in solution. They absorb on drug and mask the bitterness of drug substance. These substances, usually prepared in the form of beads, are *ion-exchange resins* and are insoluble in water. The resins may be either cation exchangers in which the resin ionisable group is acidic, for example, sulfonic, carboxylic (XVI) or phenolic groups, or anion exchangers in which the ionisable group is basic, either amine or quaternary ammonium groups. The equations describing the equilibria involved are [48].

Cation - exchange resin.
Re-COO-H+ + Basic drug+ → Re-COO-Drug+ + H+
Anion - exchange resin.
Re-N(CH3)3+3Cl- + Acidic drug → Re-N(CH3)3+ 3 Drug- + Cl-

They have the ability to exchange their labile ions for ions present in the solution with which they are in contact. Upon ingestion, drugs are most likely eluted from cation exchange resins by H+, Na+ or K+ ions and from anion exchange resins by Cl-, as these ions are most plentiful available in gastrointestinal secretions, followed by diffusion of free drug molecule out of resins.

Strong acid cation resins (sulfonated styrenedivinyl benzene copolymer products) can be used to mask the taste of basic drugs having bitter taste; as they function through out the entire pH range. Weak acid cation exchange resins function at the pH values above 6.
Similarly, strong base anion exchange resin function throughout the entire pH range, while the weak base anion exchange resins function well below pH 7.0 [70].

Typical reactions involved in the gastrointestinal fluids may be envisaged as follows:

**In the stomach**

Re-COO-Drug + HCl → Re-COOH + Drug Hydrochloride
Re-N(CH3)+3 Drug + H3 → Re-N(CH3) 3 Cl + Acidic drug

**In the intestine**

Re-COO-Drug + NaCl → Re-COONa + Drug Hydrochloride
Re-N(CH3)+3 Drug + NaCl → Re-N(CH3) 3 Cl + Sodium salt of drug

The most frequently employed polymeric network used is a copolymer of styrene and divinyl benzene (DVB). Apart from this other polymers such as those of acrylic and methacrylic acid crosslinked with divin benzene and containing appropriate functional groups, have been used as ion exchange drug carriers[49, 50].

The selection of ion-exchange resins for taste masking is governed by:

- Its functional group properties and mean concentration of exchangeable group.
- It’s swelling ratio.
- Its biocompatibility and biodegradability.

Drug release from ion exchange resin depends upon two factors

1. The ionic environment (i.e. pH and electrolyte concentration) within the gastrointestinal tract.
2. The properties of resin.

Drug molecules attached to the resins are released by appropriate charged ions in the gastrointestinal tract, followed by diffusion of free drug molecules out of the resin.

**Exchange capacity**

The exchange capacity of an ion exchange resin refers to the number of ionic sites per unit weight or volume (meq./gram or meq./mL). Sulfonic acid resin derived from polystyrene matrix have lower exchange capacities, about 4 meq/gm, than carboxylic acid resin derived from acrylic acid polymer, about 10 meq/gm, because of bulkier ionic substituents of sulfonic acid resin and polystyrene matrix.[51]

Weak acid cation exchange resins have a pKa value of about 6, so that at pH 4 or above their exchange capacity tends to increase. Ionisation of weak acid cation exchange resin occurs to an appreciable extent only in alkaline solution, i.e., in their salt form. This is reported that their exchange capacity is very low below pH 7 and moderately constant values at pH above about 9.

The rate of ion exchange is influenced by the permeability of the solvent and solute through the pores of the resin, whose number and size are influenced by the amount of crosslinking. The diffusion path length is obviously also related to the size of the resin particles.[52, 53]

**Recent trends**

Some recent examples to the use of ion exchange resins in taste masking of bitter drugs are mentioned in table 6.

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**Table 6: Shows Literature report on taste masking by ion exchange resins [54-63]**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage form</th>
<th>Resin used</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine Phosphate</td>
<td>-</td>
<td>Indion cation exchange resin</td>
<td>54</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>-</td>
<td>Lewatit CNP</td>
<td>55</td>
</tr>
<tr>
<td>Dextromethorphan hydrobromide</td>
<td>Dry/liquid suspension</td>
<td>Carbomer 934</td>
<td>56</td>
</tr>
<tr>
<td>Ephedrine hydrochloride</td>
<td>-</td>
<td>Indion CRP 244/254</td>
<td>57</td>
</tr>
<tr>
<td>Erthyromycin, clarithromycin</td>
<td>Liquid suspension</td>
<td>Carbomer 934</td>
<td>58,59</td>
</tr>
<tr>
<td>Orfibloxacin</td>
<td>Dry/liquid suspension</td>
<td>Amberlite IRP 64/69</td>
<td>60</td>
</tr>
<tr>
<td>Panacetin hydrochloride</td>
<td>Liquid suspension</td>
<td>Amberlite IRP 80</td>
<td>61</td>
</tr>
<tr>
<td>Ranitidine hydrochloride</td>
<td>Chewable tablet</td>
<td>Amberlite IRP 69/88</td>
<td>62</td>
</tr>
<tr>
<td>Remacemide hydrochloride</td>
<td>Dry/liquid suspension</td>
<td>Amberlite IRP 64</td>
<td>63</td>
</tr>
</tbody>
</table>

Interaction of amine drugs with polycarboxylic acid ion exchange resin [59-64] indicated that these resins may be quite useful in taste coverage. These studies indicated that saliva, with an average pH of 6.7 and a cation concentration of 40meq/L would only elute a limited percentage of drugs from adsorbate. However rapid elution would occur as soon as the adsorbates are exposed to the low pH of the stomach. The particle coating of polycarboxylic acid ion exchange resin adsorbrates can also be considered as a method for achieving taste coverage. This is beneficial because of the taste coverage ability of the uncoated adsorbate. Some literature reports on taste masking by ion exchange resins are given in table 7.

**Table 7: Shows more literature report on taste masking by Ion exchange resins [41, 65, 54-63, 66-68]**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Commercial resin used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin stearate</td>
<td>Macrolide antibiotic</td>
<td>Amberlite IR 120, Dowex 50, Indion 244</td>
</tr>
<tr>
<td>Dicyclomine hydrochloride</td>
<td>Anti Spasmotic</td>
<td>Amberlite IR 120, Dowex 50, Indion 244, Kyron T-154, Purolite C 100 HMR</td>
</tr>
<tr>
<td>Spiramycin, Dimenhydrinate, Roxithromycin, Levocetirizine, Norfloxacin, Ofloxacin</td>
<td></td>
<td>Amberlite IRP 50, Indion 204, Puroline C 102 DR, KyronT-104, Doshion P 544 (R)</td>
</tr>
<tr>
<td>Metronidazole, Azithromycin, Quinine sulphate, Paracetamol, Erdoxetine</td>
<td></td>
<td>Amberlite IR 4B, Dowex 2</td>
</tr>
<tr>
<td>Bufomedil</td>
<td>Vasodilator</td>
<td>Amberlite IRP 69</td>
</tr>
<tr>
<td>Chlorpheniramine maleate</td>
<td>Anti histamines</td>
<td>Indion CRP 244, Indion CRP 254</td>
</tr>
<tr>
<td>Clopidogrel sulphate</td>
<td>Anti platelet drug</td>
<td>Water soluble cation exchange resin with sulfonic acid groups</td>
</tr>
<tr>
<td>Donepezil chloride</td>
<td>Indirect Parasympathomimetic agent</td>
<td>Anionic polymer and PVP</td>
</tr>
<tr>
<td>Sildenafil citrate</td>
<td>Vasodilator</td>
<td>Anionic polymers (Carragenan, xanthan gum, dextran sulphate)</td>
</tr>
</tbody>
</table>
Regulatory aspects [71][77]

The FDA has the responsibility to define conditions under which safe food additives may be used in the production and preparation of foods and beverages. These conditions are written in the Code of Federal Regulation (CFR), title 21, part 173 (secondary direct food additives permitted in food for human consumption). Section 25 of this part deals specifically with the use of ion exchange resins. The three major conditions spelled out by this law are:

1. The resins must be one of a preapproved generic list of resin compositions (listed in 21 CFR 173.25), of which the ingredients used to produce the resins comply with FDA food additive regulations;
2. The resin must be 'subjected to pre use treatment by the manufacturer and/or user in accordance with the manufacturer's directions';
3. The resin must be 'found to result in no more than 1 part per million of organic extractives.

Some of the regulatory aspects of ion exchange resins produced by Ion Exchange (India) Limited have been mentioned;

INDION 204 - weak acid cation exchange resin

INDION 204 is a high molecular weight cross linked polymer. It is therefore not absorbed by body tissue and is totally safe for human consumption. It does not have any pronounced physiological action at recommended dosage levels and is definitely non-toxic.

Experiments on mice have shown LD 50 value of INDION 204 to be approximately 4,500 - mg/kg body weight.

INDION 214- weak acid cation exchange resin

INDION 214 is a high molecular weight polymer. It is therefore not absorbed by body tissues and is totally safe for human consumption.

Experiments on mice have shown LD 50 value of INDION 214 to be approximately 10,000 mg/kg body weight.

INDION 234 and INDION 234 S- weak acid cation exchange resin

They are high molecular weight polymer. It is not absorbed by body tissue and is totally safe for human consumption. Tests for toxicological tolerance show that it does not have any pronounced physiological action at recommended dosage and is definitely non-toxic. Experiments on mice have shown LD 50 value for INDION 234 to be approximately 10,000 mg/kg body weight.

INDION 254-Strongly acidic cation exchange resin

They does not have any pronounced physiological action at recommended dosage level and is definitely non-toxic. Experiments on mice have shown that the LD50 values to be approximately 10,000 mg/kg body weight.

INDION 264- Weak acid cation exchange resin

Not absorbed by body tissues and is totally safe for human consumption. Experiments on mice have shown LD 50 value of INDION 264 to be approximately 4,500 mg/kg body weight.

INDION 464- Weakly acidic cation exchange resin

Experiments on mice have shown LD50 value of INDION 464 to be approximately 5,000 mg/kg body weight.

Formation of inclusion complexes

Inclusion complex is a 'host-guest' relationship in which the host is complexing agent and guest is the active moiety. The complexing agent is capable of masking bitter taste either by decreasing its oral solubility or decreasing the availability of drug to taste buds. Vanderwaal forces are mainly involved in inclusion complexes.[72-76]

β- Cyclodextrin is widely used complexing for taste masking of drugs due to its sweet taste and is non toxic in nature. Cyclodextrin (CDs) are enzymatically modified starches. Their glucopyranose units form a ring: α-CD a ring of 6 units; β-CD a ring of 7units; and γ-CD a ring of 8 units. Figure 1 gives a diagram of the structure of beta cyclodextrin [87].

![Fig. 1: Structure of cyclodextrin](image)

The 'ring' is cylindrical, the outer surface being hydrophilic and the internal surface of the cavity being nonpolar. Appropriately sized lipophilic molecules can be accommodated wholly or partially in the complex, in which the host/guest ratio is usually 1:1, although other stoichiometries are possible, one, two or three CD molecules complexing with one or more drug molecules[87].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Dosage form</th>
<th>Complexing agent used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc acetate dehydrate</td>
<td>Recover zinc deficiency</td>
<td>Oral liquid</td>
<td>Anethol-β-cyclodextrin complex and saccharin</td>
</tr>
<tr>
<td>Carbamazepine citrate</td>
<td>Local anaesthetic</td>
<td>Oral liquid</td>
<td>Cyclodextrin</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>NSAID</td>
<td>Solution</td>
<td>Hydroxypropyl β-cyclodextrin</td>
</tr>
<tr>
<td>Gymnema sylvestre</td>
<td>Anti-diabetic</td>
<td>Oral liquid</td>
<td>(β-cyclodextrin, chitosan)</td>
</tr>
<tr>
<td>Dioscin</td>
<td>CVS disorders</td>
<td>Granules</td>
<td>β-cyclodextrin</td>
</tr>
<tr>
<td>Benexate hydrochloride</td>
<td>Anti ulcer</td>
<td>Granules</td>
<td>β-cyclodextrin</td>
</tr>
<tr>
<td>Metronidazole benzoate</td>
<td>Anti bacterial</td>
<td>Syrup</td>
<td>γ-cyclodextrin</td>
</tr>
<tr>
<td>Hexididine</td>
<td>Anti bacterial</td>
<td>Syrup</td>
<td>β-cyclodextrin</td>
</tr>
<tr>
<td>Zicpropl</td>
<td>Anti tussive</td>
<td>Syrup</td>
<td>β-cyclodextrin</td>
</tr>
<tr>
<td>Guaiacol</td>
<td>Anti diarrhea</td>
<td>Syrup</td>
<td>β-cyclodextrin</td>
</tr>
<tr>
<td>Levosulpiride</td>
<td>Anti psychic</td>
<td>Syrup</td>
<td>β-cyclodextrin</td>
</tr>
<tr>
<td>Chloroquine phosphate</td>
<td>Anti malarial</td>
<td>Chewable tablet</td>
<td>Eudragit-S-100</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>Anti emetic</td>
<td>Chewable tablet</td>
<td>Eudragit-S-100</td>
</tr>
</tbody>
</table>

Bitterness elimination is depended upon the extent of complexation of guest molecule with host, value of complex association constant temperature and the host/guest ratio. For bitter drug forming a 1:1 complex with cyclodextrins, more than 99 % of the bitter drug is complexed with cyclodextrins and as the complexed molecule cannot react with the taste bud in the buccal
cavity, no bitter taste perceived[88] and suppression of bitter taste by cyclodextrin was in increasing order of alpha, gamma and beta cyclodextrin [89].

Carbapentane citrate can be formulated in palatable liquid formulation with 50% reduced bitterness by forming 1:1 complex with cyclodextrin. Similarly a 1:11 to 1:15 inclusion complex of ibuprofen and hydroxy propyl-β-cyclodextrin can be formulated as palatable solution[78].

Bitter amine drugs such as chloroquine phosphate can be treated with tannic acid for taste abatement purpose[90]. Bitter taste of dimethyldiuranate can be masked by forming a porous drug-polymer matrix with an copolymer having a plurality of carboxylic acid and ester groups, e.g., Eudragit S-100 [5]. A list of complexing agents used for taste masking of certain bitter drugs are given in Table 8.

Recent trends

Kleptose ® HPBCD (Hydroxy propyl beta cyclo dextrin) from Roquette Inc. can increase the taste masking ability, solubility and bioavailability. They are better than native BCD. [96]

KLEPTOSE® Linecaps

Roquette offers a new taste-masking technology: KLEPTOSE® Linecaps uses a pea maltodextrin for masking the bitter taste of drugs by decreasing the overall amount of drug particles exposed to the taste buds. The efficiency of taste masking by amylase molecules is comparable with that of cyclodextrins, the optimal choice depends on the structure of the API[92][93].

The linear and soluble amylase fraction in the maltodextrin enables the formation of inclusion compounds as required for taste masking and other applications. Amylose acts as helical structures, and like a cyclodextrin, these bear a hydrophilic external surface and a hydrophobic internal cavity, created by the presence of glycosidic ether bonds. This cavity enables amylase to mask the bitter or unpleasant taste of drugs by decreasing the amount of drug exposed to taste buds.

The secondary structure of amylase is given in the Figure 2[94].

**Regulatory Aspects**

Cyclodextrins have regulatory restrictions especially in paediatric formulations[91].

Malto dextrins have no such regulatory restrictions and is in compliance with EU general food law 17/2002 and Current edition of the European Pharmacopeia[96]. With an expected LD 50 about greater than 5000 mg/kg[97]. It’s a readily digestible carbohydrate with a nutritive value of approximately 4 k cal/g. And is regarded as non-irritant and non toxic material. This is listed in GRAS. Included in non parenteral medicines licensed in the UK.[98]

**CONCLUSION**

To ensure palatability of active ingredients in paediatric formulation requires masking of undesirable bitter taste. And this need is too high for pharmaceutical companies to make patient compliance for their products. At the same time it should not compromise with safety and efficacy while in the race of developing new paediatric formulation.

**REFERENCE**

3. N. Roquette: KLEPTOSE® OPBD/ NICHID PFI Workshop November 1–2, 2011 Final 12-21-11, pg no 18

**Fig. 2: Secondary structure of amylase**

Smoothenol®[95]

Smoothenol® is a portfolio of natural technology systems that enhance palatability of beverages by masking the undesirable off-notes and aftertaste commonly associated with sweeteners, caffeine, vitamins and minerals, nutraceutical and functional ingredients, and beverage bases. It's a product from Sensient ® Flavours LLC.

The main ingredients of it are Potato Maltodextrin, Silicon Dioxide (Anticaking agent) and natural flavor. It would not mask the entire bitterness but will curtail the sensation for the time it is taken in mouth. Smoothenol® works by modifying the consumer sensory perception and essentially eliminating bitter off-notes and astringency that may be present when formulating with non-nutritive sweeteners such as stevia.

91. Roquette University; Ashish A.Joshi, Ph.D- Pediatric formulations-presentation "How sweet is the medication" A robust encapsulation solution with focus on pediatric dosage delivery.


94. Fig.2 from Mathews and van Holde: Biochemistry 2/e. Copyright of Benjamin/Cummings Publishing Co.Inc.

95. www.sensientflavors.com gives details on smoothenol taste masker.

