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TASTE MASKING: A NOVEL APPROCH FOR BITTER AND OBNOXIOUS DRUGS

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ABSTRACT: Taste is mainly a function of taste buds in the mouth. In the formulation for pediatric & geriatric, bed ridden & non-cooperative patients the main challenge to the compounding pharmacist is to mask the taste of obnoxious and bitter drugs, result is patient not receiving the optimal therapeutic value of their medication. Taste masking is the main factor in the development of the dosage form. It opens the doors for new inventions and patents. Many techniques have been developed which not only improve the taste of molecule but also the formulation and performance of the molecule. The main objective of present review is to explore different method, technologies and evaluations to mask the obnoxious taste of drugs, so that patients can use these drugs without hesitation of taste.

Introduction:

Taste masking of the drugs which are bitter in taste has been proved to be accepted for pediatric and geriatric patients. The bitterness of pharmaceutical medicines plays a critical role in patient compliance, as the oral administration of bitter drugs is often hampered by their unpleasant taste which leads to non-compliance and further worsening of diseased condition [1]. Unwillingness to swallow solid dosage form such as tablets is a general problem for all age groups, especially elderly and pediatrics mainly due to the physiological changes. Forty five per cent of stroke survivors, thirty three per cent of nursing home residents and sixty three per cent of cancer patients undergoing palliative care in the community or hospital report dysphagia [2]. By using various available conventional methods, for the reduction in bitterness of drugs we can also improved palatability of oral pharmaceuticals [3]. Biologically, the perceptions of taste in humans occur when molecules trigger signals in the mouth which is sent to the brain area, where a specific taste sensation is recognized. A molecule reacts with taste receptor with the help of small organs called taste buds located in the mouth mainly on the surface of tongue and gives sensation like sweet, sour, bitter and salty.

FIG:-1

These four tastes are located on different receptors on tongue, sensations for sweet are located at tip of the tongue and sensations for sour are located at sides of the tongue whereas bitterness at the back of the tongue and salty sensations are located at the sides and tip of the tongue [4]. Recently, a basic taste umami has been discovered. Umami is the fifth independent taste produced by monosodium glutamate (MSG) contained mainly in seaweed and disodium inosinate (IMP) in meat and fish. These above taste receptors that bind to molecules down by saliva transmit electrical impulses by 7th, 9th and 10th cranial nerves to these areas of brain which participate in perception of taste.

Among various approaches two are commonly used to diminish the bitter taste of drug [5].

1. By reducing the solubility of drug in the pH of saliva (5.6 - 6.8).
2. By altering the affinity and nature of drug which will interact with the taste receptor.

Taste masking is not an easy and simple procedure efforts are required before bitter drugs are acceptable for market trials. It needs number of steps. Pharmaceutical industries invest time, money and resources into developing palatable and pleasant tasting products and industries adopt various taste-masking techniques to develop an appropriate formulation. So to avoid unwanted wastage time and money, we concluded that ideal taste masking formulations should:

- Involve less equipments and processing steps.
- Effectively mask taste with as few excipients which are economically and easily available.
- Have no adverse effect on drug dissolution and bioavailability.
- Be cost effective and
- Be scalable.

Patients now expect and demand formulations that are pleasantly, or at least tolerably, flavored. Flavor enhancers are the simplest and oldest method used but this method fail to mask 90% of moieties. When these methods fail then some new conventional methods were adopted such as microencapsulation which includes coating, spray drying techniques, by chemicals, inclusion complexes with cyclodextrins, use of ion exchange resins, prodrugs and other Different techniques like liposomes, multiple emulsions etc.

Methods and technologies for taste masking include;

FLAVOURS AND SWEETNERS IN TASTE MASKING:

Pharmaceutical flavors are classified as natural, artificial, or natural and artificial which are obtained by mixing the natural & synthetic flavors. We have naturally occurring flavouring agents, which can be used in various concentrations such as Anise (3000ppm), Cardamom (550ppm), Wild cherry (50-800ppm), Lemon (1-35ppm), Orange (500ppm), and Peppermint (5000ppm). Natural flavours are comparatively less active than combination of natural and artificial in terms of quality and uniformity. Also these combinations can achieve their aim at very low concentrations. These are generally used in extracts, alcoholic or aqueous solutions, syrups or spirits [6]. These flavors are also used in formulations to mask the bitter taste and give pleasant mouth feel. Mannitol and Aspartame are most widely used excipients in formulating oral disintegrating tablet [7].

Fuisz., 1991 relates the masking of obnoxious taste of Aspirin medicated floss contains sodium phenolate as an anaesthetizing agent in addition to chocolate flavor [8]. Hussain., 1991 interrelates Eucalyptus oil which is commonly used in a cough syrup formulations and in mouth washes, the bitterness was overcome by borneol or isoborneol and fenchone [9].

COATING

Coating of bitter drugs is a good application found in pharmaceutical field. This is the simplest and most feasible option to achieve taste masking. Now day's microencapsulation technique gaining much importance. Microencapsulation is a process which has been defined by Bakan in 1986 as a means of applying relatively thin coating to small particles of solid, droplets of liquid and dispersion. Effectiveness of this methodology is more and more depends upon the nature of polymer. If the polymer found to be permeable to aqueous solvents, then their effectiveness for taste masking purposes found as being less than perfect, due to drug leaching is a frequent occurrence and is therefore improved coating which is non-permeable for taste masking purposes will maintain its integrity and will not release the content in mouth but release the medication in the gastric fluid of the stomach [10]. Various inert coating agents like starch, povidone, gelatin, methylcellulose, ethyl cellulose, Hydroxy Propyl Methyl Cellulose, Bees wax, carnauba wax, acrylics and shellac etc. are used for coating drug particles [11].

Various previous methods have been employed to mask the medicaments. It includes coating of the rotogranulations with a taste masking polymer, mixture of cellulose acetate or cellulose acetate butyrate and polyvinyl pyrrolidine. Also by eudragit E100 and some hygroscopic water insoluble substances such as Al/Mg antacids as external excipients for the masking of unpleasant taste of cemitidine. In one more study, it was reported that by microencapsulating the core of tablet containing bitter actives with ethyl-cellulose, metha- acrylate co-polymers etc. these methods are proposed by U. S. Pat. No. 5,084,278 [12].

Glaxo-Group limited described a process in WO 94/08576 by first encapsulating ranitidine or a suitable salt form in a polymer matrix such as ethyl cellulose or by using a molten waxy material such as Carnauba Wax, Glyceryl tristerate or tripalmitate (high molecular weight straight chain saturated or unsaturated fatty acids, esters and alcohols) to obtain tasteless ranitidine granules with drug content of about 20%w/w and compressed into chewable tablets [13].

In a study microencapsules of Cefuroxime Axetil were prepared with various cellulosic polymers such as CAT, BPMCP-55 and UPMCP-50, having a pH dependent solubility; with the final aim to mask its taste while assuring its release in the intestinal cavity. The drug release studies and the stability assay of the encapsulated moiety demonstrated that UPMCP-55 microspheres represent a useful approach to achieve the proposed objective [14]. Also in case of Ibuprofen taste masking has been achieved by using the air suspension coating technique to form microcapsules, which comprises a pharmaceutical core of a crystalline ibuprofen and methacrylic acid co-polymer coating [15].

Spray drying which comes under microencapsulation. It is also one of the most popular techniques of coating, which converts the atomized liquid droplets into dry powders by hot air. Spray-drying is a process where a drug solution is atomized to fine droplets followed by evaporation in a stream of warm air to form dry particles [16]. The properties of the spray-dried products are controlled by both the process and formulation parameters [17].

Taste masked microspheres prepared by spray drying technique of intensely bitter drug used in management of nausea and vomiting were tested with two different polymers having different ratios. Ondansetron hydrochloride (OSH) was used in which Eudragit microspheres showed taste masking at 1:2 drug–polymer ratio and with Chitosan microspheres the taste masking was achieved at 1:1 drug–polymer ratio and better acceptance by patients [18].

One method is also reported which discloses a method for preparing a taste masked therapeutic composition which comprises spray drying a suspension of acetaminophen in a solution of an acrylic polymer in an organic solvent. Further one more study revealed that in a taste masking composition, which comprises an effective amount of spray dried spheroidal microcapsule core containing Sucralfate under about 150 microns in diameter [19-20].

Taste masking by spray-congealing technique, which uses a spray dryer, and is considered to be an effective method of taste masking, easy to industrialize, cost effective and requires no solvent. It can produce a

more dense film than other methods without moving materials for drying [21].

Table:1

S.No	Drug/active agent	Technique/formulation	Category	Reference.
1.	Gabapentin	Coating	Anticonvulsant	[22]
2.	Isoprothiolane	Spray drying and coating	Antifungal	[23]
3.	Pinaverium bromide	Coating	Used in GIT disorders	[24]
4.	Propantheline bromide	Coating	Antimuscarinic agent	[24]
5.	Ibuprofen	Air-suspension coating	NSAIDs	[15]
6.	TriprolidineHCl	Dispersion coating	Antihistamine	[25]
7.	Dimenhydrinate	Coating	Emetics	[26]
8.	Enoxacin	Granulation and coating	Used as UTI	[27]
9.	Sparfloxacin	Granulation and coating	Antibiotic	[28, 29]
10.	Ibuprofen	Retogranulation and coating	NSAIDs	[30]
11.	Aspirin	Retogranulation and coating	NSAIDs	[31]
12.	Famotidine	Retogranulation and coating	Anti-ulcer	[32]
13.	Acetaminophen	Coating	Analgesic, antipyretic	[33, 34]
14.	AmprilomeHCl	Coating	Anti-gout	[35]
15.	Roxithromycin	Granulation and coating	Macrolide antibiotic	[36]
16.	CetraxateHCl	Melt granulation and coating	Cytoprotective action	[37]
17.	Pirenzepine and Oxybutynin	Dispersion coating	Anti-ulcer action	[38]
18.	Nicorandil	Coating	Anti-anginal action	[39]
19.	Levofloxacin	Coating	Fluoroquinolone Antibiotic	[40]
20.	Isoprothiolane	Spray drying	Anti-fungal	[41]
21.	Acetaminophen	Spraying/tablet	Analgesic, antipyretic	[42]
22.	IndeloxazineHCl	Fluidized bed drying	Neuroprotective action	[43]
23.	Nizatidine	Spray drying	Anti-ulcer action	[44]
24.	Ibuprofen	Spray coating	NSAID	[45]
25.	BidemelaneHCl	Coating and spraying	Neuroprotective action	[46]
26.	Ondansetron HCL	Spray drying	Antiemetic	[18]
27.	Diphenylpyraline HCL	Spray drying	Antihistamine	[47]
28.	Cefuroxime axetil	Coating	Antibiotic	[48]
29.	Famotidine	Coating	Antihistamine	[49]
30.	Erthromycin	Coating	Antibiotic	[49]

Microencapsulation by coacervation-phase separation process consists of three steps carried out under continuous agitation;

- Formation of three immiscible chemical phases.
- Deposition of coating.
- Rigidization of coating.

Coating done by coacervation process also shows better results. In one study Oral Disintegrating Tablets containing drug core particles microencapsulated by co-acervation with a taste masking membrane comprising a water insoluble polymer in combination with one or more pore-formers which are practically insoluble in saliva and soluble in gastric acid [50]. Microencapsulated beclamide, in which anhydrated sodium sulphate was used as coacervating agent, was masked by a simple co-acervation method-using gelatin [51].

Taste masking of Tinidazole was achieved by microencapsulation using amino alkyl methacrylate co-polymers (Eudragit E100) employing the solvent evaporation technique [52].

Taste masking of Ornidazole was achieved by microencapsulation using amino alkyl methacrylate copolymers (Eudragit E100) employing the solvent evaporation technique [53].

MOLECULAR COMPLEXES OF DRUG WITH OTHER CHEMICALS:

Molecular complexes can minimize the intensity of bitterness by modifying the solubility and absorption of drug by the formation of complex. This usually decreases the intensity of bitterness of drugs. Higuchi and Pitman reported that caffeine forms complexes with organic acids that are less soluble than xanthenes sand as such can be used to decrease the bitter taste of caffeine [54].

INCLUSION COMPLEX FORMATION:

Inclusion complex formation not only masked the taste of the molecule but said to result in improved solubility of the drug and more efficient absorption of the drug by the body. Cyclodextrins are mainly used for inclusion complex formation, the drug molecule fits into the cavity of a complexing agent i.e. host molecule forms a stable complex. The Cyclodextrins wraps the bad tasting molecule to inhibit its interaction with the taste buds, or it interacts with the gatekeeper proteins of the taste buds [55]. Cyclodextrins (CDs) are cyclic oligosaccharides made up of six to twelve D-glucopyranose monomers connected at 1 and 4 carbon atoms. Industrially produced CDs are crystalline, homogeneous non-hygroscopic substances built up from glucopyranose units. The αCD comprises 6, the βCD 7 and the γCD 8 glucopyranose units. Carbon conformation in which the glucopyranose units all secondary hydroxy groups are located on the wider edge of the ring, whereas all the primary ones are placed on the narrower edge. The ring in reality is a conical cylinder, into which the outer surface of this cone is hydrophilic and the axial cavity is hydrophobic. Most widely used complexing agent for inclusion type complexes is β Cyclodextrins [56].

US patent no. 5,024,997 reports Ibuprofen and hydroxypropyl β Cyclodextrin relates to a palatable ibuprofen aqueous base solution for oral administration [57]. Patient acceptance especially in the pediatric and geriatric population has been improved by masking the bitter taste of Oseltamivir Phosphate (OP) an anti influenza drug by β Cyclodextrin [58]. Primaquine phosphate, an anti-malarial drug with an extremely unpleasant taste was masked by β Cyclodextrin and a suspension powder (cachets) was formulated of this taste masked drug [59].

Fig:2

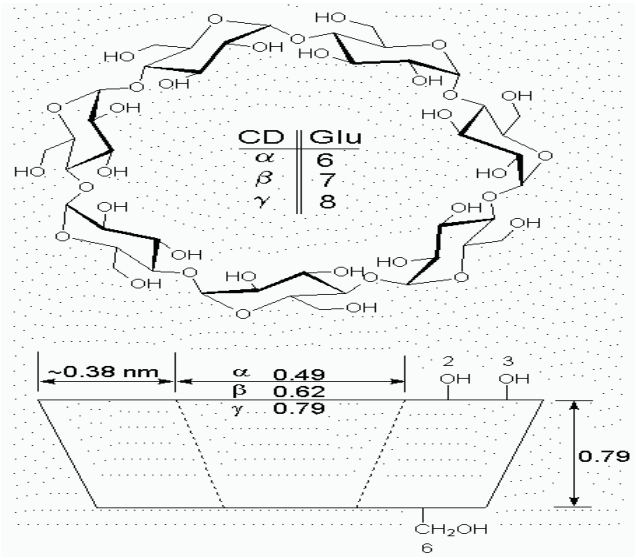

Fig:3

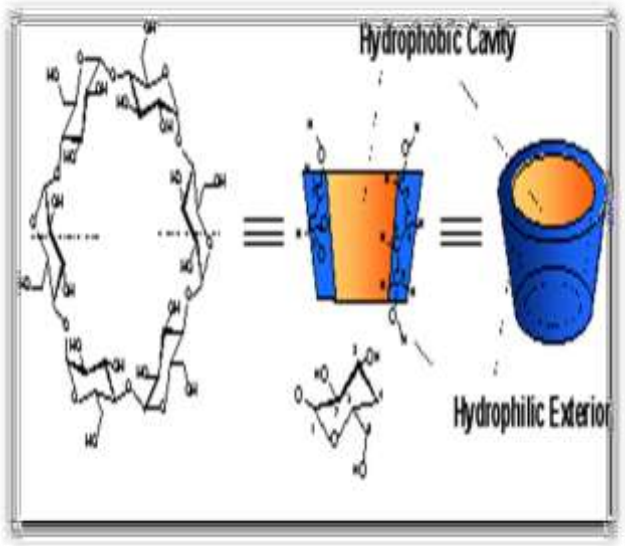

Table:2

S.No	Drug/active agent	Resin/complexing agents	Category	Reference
1.	Zinc acetate dehydrate	Anethol- β–cyclodextrin complex and saccharin	Recover zinc deficiency	[60]
2.	Carbetapentane citrate	Cyclodextrin	Local anesthetic	[61]
3.	Ibuprofen	Hydroxypropyl β-cyclodextrin	NSAID	[57]
4.	Gymnema sylvestre	β-cyclodextrin	Anti-diabetic	[62]
5.	Dioscin	β-cyclodextrin	Cardiovascular disorders	[63]
6.	Benexate	β-cyclodextrin	Antiulcer	[64]
7.	Metronidazole benzoate	-cyclodextrin	Anti bacterial	[65]
8.	Hexitidine	β-cyclodextrin	Anti bacterial	[66]
9.	Zipeprol	β-cyclodextrin	Anti-tussive	[67]
10.	Guaiacol	β-cyclodextrin	Anti diarrhetic	[68]

SPERONIZATION TECHNIQUE:

The extrusion/spheronization process was first introduced to the pharmaceutical industry in 1964 with the invention of the marumerizer [69]. Extrusion-Spheronization produce pellets/beads of uniform size with maximum drug loading capacity. Extrusion–Spheronization is a multistep process Involving dry mixing, wet granulation, extrusion, spheronization, drying, and screening. A process of wet mass extrusion followed by spheronization to form spherical particles namely called as Spheroids, Beads, pellets depending upon the material as well as process used for extrusion Spheronization [70]. An advantage touted for extrusion spheronization is the formation of more spherical pellets compared to wet granulation [71].

Mouth dissolved tablets of Tramadol HCl by spheronization technique include taste masked tablet with maximizing the porous structure, into which factorial design was used to optimize the formulation in which sphericity and the disintegrating parameters were dependent variables [1].

Rapidly Disintegrating tablet was prepared by extrusion Spheronization method in which intensely bitter taste of Metoclopramide Hcl was masked [72].

Augello et al., 1999 relates a chewable pharmaceutical composition into which active ingredients such as; Ibuprofen, ketoprofen, fenoprofen, calcium naproxen, and/or combination thereof is masked by the physical form of composition which is blended with a microcrystalline cellulose composition, wet granulated and formed into tasked masked spheres [73].

ION EXCHANGE RESINS (IER)

Classical and well-known approach in the development of taste masking is ion exchange resins (IER). IER are polymers that are capable of exchanging particular ion within the polymer with ions in solution that is passed through them. IER are solid and suitably insoluble high molecular weight poly-electrolytes that can exchange their mobile ions of equal charge with the surrounding medium. Drugs can be loaded onto the resins by an exchanging reaction, and hence, a drug-resin complex (drug resinate) is formed [74]. Being high molecular weight water insoluble, the resins are not absorbed by the body and are therefore inert [75]. Ion exchange can be define as a reversible process in which ions of like sign are exchanged between liquid and solid, a highly insoluble body in contact with it [76]. Synthetic ion exchange resins have been used in pharmacy and medicine for taste masking or controlled release of drug as early as 1950 [77]. For taste masking purpose weak cation exchange or weak anion exchange resins are used, depending on the nature of drugs.

Table:3

Commercial resin	Matrix	Functionality	Ionic form	Examples of Drugs
Amberlite IR120, Duoxes 50, Indion 244, PuroliteC100HMR, Kyron-T-134	Styrene DVB Polymer	SO_3H	Strong cation	Erythromycin lactate, Dicyclomine HCL etc.
Amberlite IRP 69, Indion 254, TulsionT- 344	Sodium Styrene DVB Polymer	SO_3Na	Strong cation	Ranitidine, Dextromethorphan etc.
Amberlite IRC 50, Indion 204, Purolite C102HR, Kyron -T-104, Tulsion T- 335, Duolite P144(R)	Methacrylic acid DVB Polymer	$-COOH$	Weak cation	Spiramycin, Ranitidine, Dextromethorphan, Dimenhydrinate, Roxithromycin, Levocetirizine, Dicyclomine Hcl, Norfloxacin, Ofloxacin etc.
Amberlite IRP88, Indion 234,Tulsion T-330,Kyron-t-134	Methacrylic acid DVB Polymer	$-COOK$	Weak cation	Ciprofloxacin, Chloroquine phosphate, Metronidazole, Azithromycin, Quinine sulphate, Paracetamol, Ephedrine, Doxylamine Succinate etc.
Amberlite IR400, Indion 454, Duoxes 1, Duolite AP 143.	Styrene DVB Polymer	N^+R_3	Strong anion	
Amberlite IR4B, Duoxes 2	Styrene DVB Polymer	N^+R_2	Weak anion	

A palatable liquid formulation of taste mask drug Tinidazole (TNZ) by novel ion exchange resin method in this formulation Polystyrene matrix exchange and release the drug as soon as they come in contact with saliva are highly desirable for pediatric and geriatric population. Such Oral Disintegrating Drug Delivery Systems obviating the requirement of water for administration. An orodispersible resin has been used to mask the bitter taste of TNZ [78].

Solid dosage forms that usually dissolve or suspended in mouth and rapidly disintegrate tablet of taste masked doxylamine succinate using ion exchange method in which weak cation exchange Indion -234 was used [79].

An orally disintegrating tablet was formulated of Levocetirizine Dihydrochloride using ion exchange method in which drug resin complex was prepared by kneading method. Relatively acceptable taste was achevied with both Indion 204 and Tulsion 335 [80].

Molecular complex was prepared of Ciprofloxacin with polacrillin potassium i.e. Indion 234 with efficient drug loading was, the drug resin complex with ratio 1:1.3 was characterized by infrared spectroscopy, thermal analysis and X-ray diffraction pattern [81].

TASTE MASKING BY PRODRUG APPROACH

Prodrugs are defined as therapeutic agents that are inactive moieties but on biotransformation liberate the pharmaceutically active parent metabolites. By changing the molecular configuration of the parent molecule, the magnitude of a bitter taste response or taste receptor-substrate adsorption constant may be modified. Prodrugs can be used to increase or decrease the aqueous solubility, mask bitterness, increase lipophilicity, improve absorption, decrease local side effects, and alter membrane permeability of the parent molecule [82]. Tasteless/bitterless prodrugs of opioid analgesics and antagonists were formulated for improved buccal delivery, when administered as prodrugs; the bioavailability was improved without visible adverse effects [83]. Prodrug with improve taste masking [5, 84].

Table:4

Clindamycin	Alkyl ester
Chloramphenicol	Palmitate or phosphite ester
Triamcinolone	Diacetate ester
Erythromycin	Alkyl ester
Lincomycin	Phosphate or alkyl ester

Tetracyclin	3,4,5-Trimethoxy benzoate salts

TASTE MASKING USING LIPOSOME'S AND MULTIPLE EMULSION

Entrapment method of masking the obnoxious taste of therapeutic agent is to entrap them into Liposomes. Liposomes are carrier molecules comprising lipids most often in spherical molecules with several layers of lipid, and the drug or biological agent is carried within the lipid molecule. Oils, surfactants, polyalcohols and lipids effectively increase the viscosity in the mouth due to which the decrease in contact between the bitter medicament and the taste receptors, thus improving the overall taste masking efficiency. Liposomes are simple microscopic vesicles in which an aqueous volume is entirely closed by a membrane composed of lipid molecules, lipid bilayers mainly composed of natural or synthetic phospholipids. Selective inhibition of bitter taste of various drugs by phospholipids such as phosphatidic acid, phosphatidylinositol, soy lecithin, has been reported [85]. The bitter taste of Chloroquine phosphate in HEPES (N-2-hydroxyetylpiperzine-N'-2- ethane sulfonic acid) buffer was masked at pH 7.2. by incorporating into a liposomal formulation prepared with egg phosphatidyl choline [86].

Multiple emulsions is also a good approach for taste masking of drugs prepared by dissolving the drug moiety in the inner aqueous phase of w/o/w emulsion under conditions of good shelf stability. This system could be used for controlled-release delivery of pharmaceuticals multiple emulsions of the oil-in-water-in-oil (o/w/o) type are w/o emulsions in which the water globules themselves contain dispersed oil globules; conversely,

water-in-oil-in-water (w/o/w) emulsions are those where the internal and external aqueous phases are separated by the oil. Both w/o/w and o/w/o multiple emulsions of Chloroquine phosphate have been prepared and reported to be partially effective in masking the bitter taste of drug [87].

EVALUATION OF TASTE MASKING:

As we all know that the medicines are the only way for human beings to get well from the disease. But these medicines are not always compatible, they have to make it, by incorporating an agent which can improve the palatability of these medicaments and provides the patient with a pleasant product experience. Next step is to determine what additional functional excipients are required for the final dosage form. These include sweetners, flavouring agents and super-disintegrant. Before using these agents all the preformulation parameters have to satisfy. All the physical, chemical and therapeutic compatabilities with the taste masking agent must be optimized.

Soutakagi., et al. discovered a multichannel taste sensor (E-tongue) which is somewhat similar to human gustatory sensation [88]. This sensor consists of transducer, which is composed of several kinds of lipid/polymer membrane with different characteristics. Taste information is transformed into a pattern composed of electrical signals of membrane potential of the receptor part. It was previously reported to record the suppression of bitterness of quinine and acesulfame K, as a bitterness inhibitor by using multi channel taste sensor [89]. E-tongue provide a fast, objective and simple assessment of oral formulations such as chewable tablets, liquid, rapid dissolve tablets and films, oral dispersive lozenges, sublingual delivery methods, and nasal delivery products which is highly correlated with the organoleptic taste panel methods. This method can be expected to provide new automated method to measure the strength of drug substance in place of sensory evaluation.

In case of microsphere evaluation can be done by determining the rate of release of the drug from the microspheres. Same method is followed for ion exchange resin, the drug release rate can serve as an index of the degree of masking achieved. Recently, a taste analyzing system manufactured by Alpha MOS has become commercially available. The taste sensor consists of silicon transistors with an organic coating that governs sensitivity and selectivity of each individual sensor. The life of the sensors could last as long as 1 year.

Under Other methods we have evaluation by a trained flavor profile panel and time intensity method in which a sample equivalent to a normal dose was held in mouth for 10 seconds. Bitterness level are recorded immediately and assigned values between 0-3 [90].

CONCLUSION

In addition to oral drug delivery, taste masked drug delivery research is gaining importance and commercial success for the quality of treatment provided to suffering patients, especially children. As evidenced by the number of patents and technological developments we made an attempt that an ideal taste masking is widely accepted in the development of more palatable and acceptable dosage forms which not only lead to better patient compliance but with an ultimate clinical output.

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