IJPSR (2013), Vol. 4, Issue 11 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 24 June, 2013; received in revised form, 19 August, 2013; accepted, 09 October, 2013; published 01 November, 2013

GUSTATORY SYSTEM AND MASKING THE TASTE OF BITTER HERBS

Vinita Kale, Chetan Tapre and Abhay Ittadwar

Department of Pharmaceutics, Gurunanak College of Pharmacy, Nagpur, Maharashtra, India

Keywords:

Bitter herbs**,** Gustatory system, Transduction mechanisms for Bitters, Taste masking techniques, Evaluation of taste

Correspondence to Author:

Vinita Kale

Department of Pharmaceutics, Gurunanak College of Pharmacy, Nagpur, Maharashtra, India

E-mail: kvinita@rediffmail.com

ABSTRACT: The oral route is the most easy and favorable route of drug administration. The development of oral formulations containing bitter herbs has widely been required in pharmaceutical and herbal industry. The human gustatory system is capable of identifying five major taste qualities: sweet, sour, salty, bitter and umami (savory). Different receptors and transduction mechanisms are involved in the detection of each taste quality. Many efforts have been focused to improve the palatability in these products that has prompted in the development of numerous techniques of taste masking. Once a method for taste masking is adopted, it becomes apparent to evaluate the effectiveness of the taste masked product. The major hurdle in evaluation of measuring the effectiveness of taste masking is that the taste is a highly subjective property and it varies demographically and with the age and gender. This communication gives a brief account of gustatory system, the receptor and transduction mechanism of bitter taste and various techniques used in taste masking of the bitters. The review also reveals the *in-vitro* and *in-vivo* methods for evaluating taste masked efficiency of developed product. Finally, the review concludes that proper choice of method for taste masking method is essential and it might depend on the properties of the herbs.

INTRODUCTION: In herbal medicine there is a class of herbs called bitters. Bitters or healing herbs are a diverse group of chemical compounds that share the common characteristics of bitter taste. Traditionally it is a flavor that is universally disapproved to characterize unpleasant sensation, harshness and feelings extremely difficult to bear. Yet it is also flavor used in culture the world over to strengthen digestion, cleanse the body and built vitality, in short considered as an ingredient essential for good health.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.4(11).4118-24

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.4(11).4118-24

The patient experience matters when it comes to how herb/ drug product is delivered. If herbs/ drug leave a bitter or otherwise unpleasant taste in the mouth, the patient may reject the product leading healthcare providers to look for alternatives or to mask the bitterness becomes essential. Masking bitterness is perhaps the number one candidate for taste modifiers. Taste masking of bitters has been the subject of substantial research. In order to get the reasoning behind this research, a basic understanding of anatomy and physiology of taste is necessary.

Gustatory system of human being: Human body contains several chemoreceptors that can respond to chemicals. The two major chemoreceptive senses are smell (olfaction) and taste, also called as gustation. There are many flavors that can be experienced.

However, there are only 5 basic tastes- sweet, salty, bitter, sour and umami (delicious). Some taste preferences are inborn for example, natural preference for sweet while bitter substances are rejected.

Taste receptor cells reside primarily in the tongue but also are in significant number in the soft palate, oesophagus, epiglottis and larynx. The tongue has three types of papillae (i.e. taste sensitive structures) that contain taste buds, these are;

(1) Fungiform papillaa, located at most anterior part of the tongue and appear as red spots;

(2) Foliate papillae, present at the edge of the tongue; and

(3) Circumvallate papillae present at the back of tongue (**Fig. 1**) [1].

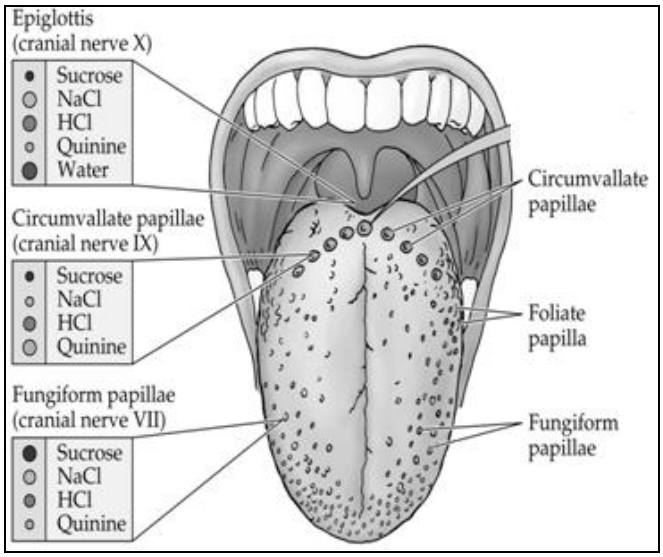

FIG. 1: PAPILLAE ON TONGUE

The taste receptors are clustered in organelles called as taste buds. Each taste bud contains basal cells, taste receptor cells and supporting cells (**Fig. 2**).

The basal cells differentiate into receptor cells that are continually renewed every 10- 14 days. The receptor cells (50- 150) are arranged like segment of an orange and contains sites of sensor transduction. Each taste bud contains afferent (sensory) nerves.

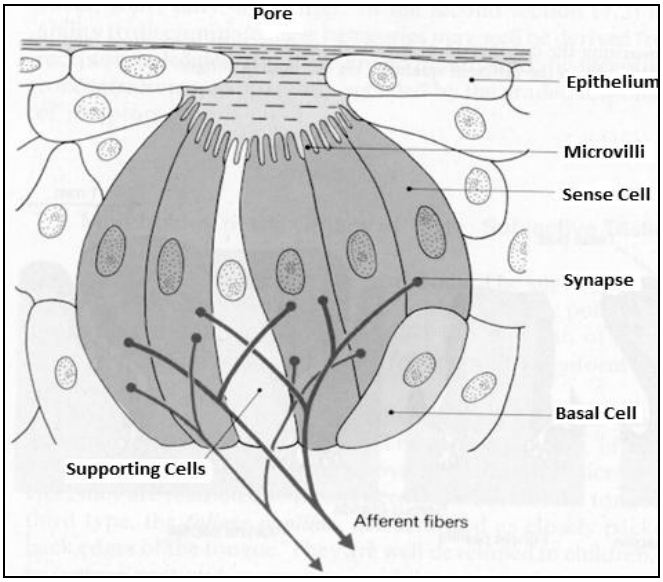

FIG. 2: TASTE BUD

How bitter taste is perceived: When taste receptor is activated by the bitter or otherwise appropriate chemical on dissolution, its membrane potential changes, called as receptor potential. As a result, depolarization of receptor potential occurs that causes Ca^{++} to enter the cytoplasm (**Fig. 3**). The Ca^{++} subsequently causes the release of neurotransmitter [2].

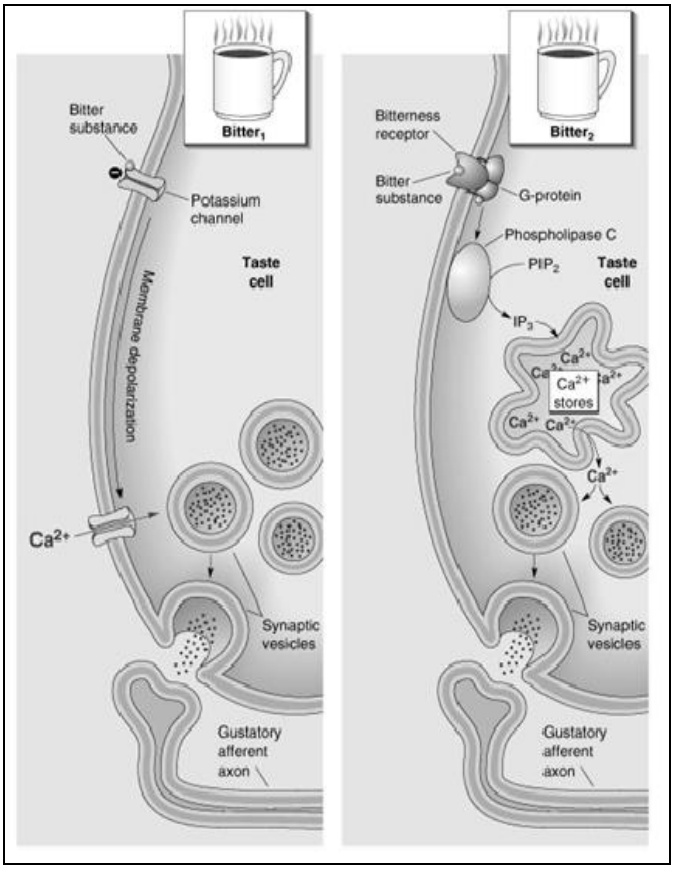

FIG. 3: RECEPTORS FOR BITTER TASTE

The taste ligand may either bind or pass as summarized below:

a. Pass directly through an ion channel (salt and sour)

b. Bind to and block ion channels (sour and bitter)

c. Bind to and open ion channels (some sweet amino acids)

d. Bind to membrane receptors that activate 2nd messenger systems that in turn open or close ion channels (sweet and bitter).

Masking of bitter taste of herbs: In order to effectively mask a taste, developers first need to understand the type of interactions that can occur in a composition/formulation matrix, as well as interactions occurring over the tongue. On the basis of perception, taste-masking can occur at two different levels: they can occur in-mouth (peripheral interactions; e.g. taste inhibition) or at the brain level (central cognitive interactions; e.g., mixture suppression).

Therefore, the techniques used for taste-masking are also based on these two phenomena. However the third method can also to include other technologies for eliminating the source of the undesired taste, such as encapsulation or target elimination of the bitter compound. Here are described three approaches that can be used for targeted masking.

1. **Bitter Taste masking by Inhibition of receptors (Peripheral Interactions):** A number of possible interactions can happen when two compounds are placed in the mouth together. There is always possibility that one compound would interfere with taste receptor cells or taste transduction mechanisms associated with another compound, which could lead to enhancing or suppressing the taste. Many efforts have been focused on finding blockers for specific bitter taste, as it would provide a means for reducing bitter-taste. However, since there are several receptors for bitter perception, it is difficult to find a single (universal) compound that can inhibit stimulation of all the bitter taste receptors. Compounds like Zinc and Sodium salts at particular concentration have been known to mask the bitter taste [3]. Scientists have found that a lipoprotein, PA-LG made of phosphatidic acid (PA) and *β*-lactoglobulin (*β*-LG), selectively suppresses the taste responses to bitter substances [4].

   Riboflavin-binding protein (RBP) from chicken egg was also found to be a bitter inhibitor. RBP elicited broadly tuned inhibition of various bitter substances including quinine-HCl, naringin, theobromine, caffeine, glycyl-L-phenylalanine (Gly-Phe), and denatonium benzoate, whereas several other proteins, such as ovalbumin (OVA) and β-lactoglobulin, were ineffective in reducing bitterness of these same compounds [5]. Research in this area has recently focused on receptor-based assays, where different compounds are tested directly on the target receptor and are screened for either activation or suppression of the taste signal.

2. **Bitter Taste masking by using Mixture Suppression (Central Cognitive Interactions):** Gustatory stimulants contained in a mixture often evoke responses different from those elicited when they are presented alone. In short, when one taste (masker) is strong enough, it can completely mask another taste (target) of different quality. This principle is exemplified in the *logenzes dosage form* where sugar is used to mask the bitter taste of a medicine. In this particular case, the sugar is not necessarily interacting with bitter receptors in the mouth; the suppression is happening at a higher level, where taste and smells are normally integrated to deliver what is known as flavor.

   Mixture suppression is taking place in the brain. But suppression is not restricted to only taste-taste interactions. One could think that if aromas are capable of enhancing certain tastes (e.g. furaneol has been shown to enhance sweet taste), then it could also be expected that certain aromas can suppress taste perception [6]. But it is not very successful for highly bitter and highly water soluble drugs. Artificial sweeteners and flavors are generally being used along with taste masking techniques for

improving characteristics of the dosage form. Cooling effect of taste masking agents such as menthol reduces the bitterness of the drug. Combination of citric acid and sodium bicarbonate with certain flavors masks the bitter taste of certain drugs like chlorpheniramine maleate and phenyl-propanolamine. Aspartame is used as prominent sweetener in providing bitterness reduction. 0.8% concentration of aspartame is effective in reducing the bitterness of 25% acetaminophen. Starch, lactose and mannitol have also exhibited taste masking properties of caffeine [7, 8].

Temporary numbing of taste buds by certain anesthetizing agents such as phenol and sodium phenolate has also been used to mask the unpleasant taste of drugs such as aspirin. This anesthetic agent numbs the taste buds sufficiently within 4 to 5 seconds and helps to mask bitter taste [9].

CO_2 producing substance like citric acid or tartaric acid with sodium bicarbonate can also reduce bitter taste of formulation. The carbonated water partly disguises unpleasant taste of saline medicaments that are administered as effervescent granules or tablet [10]. Increasing the viscosity with thickening agents such as gums or carbohydrates can lower the diffusion of bitter substances from the saliva to the taste buds. This provides a taste masked liquid preparation for administration of a relatively large amount of unpleasant tasting medicines. The composition of such a formulation comprises a taste-masking liquid base with a high viscosity induced by thickening agents such as polyethylene glycol and sodium carboxymethylcellulose [11].

Pellets of Bitters: Pellets for herbal preparation application are defined as spherical, free-flowing granules with a narrow size distribution (between 500- 1500 µm) [12]. The pelletization process consists of the agglomerates of fine powders of the herbs and excipients including the taste masking, into spherical units. The extrusion/ spheronization pelletization process comprises of five unit operations: blending, wet massing, extrusion, spheronization and drying.

During extrusion the wet mass is forced through a restricted cross- section of different sizes and types.

The extrudes so formed are broken into small cylinders with length equal to their diameter and rounded during spheronization step. At the end of the spheronization process, the wet pellets are dried.

Another important and modified method of preparing matrix pellets is using hot- melt extrusion. This method is generally used when the herbs or its actives are sensitive to the water and/or rigorous drying conditions. In this method the herbal particles and meltable materials are bound together into agglomerates.

Melt extrusion process consists of three basic steps-melting or plasticizing a solid material, shaping the molten material and solidification of material into desired shape during spheronization [13, 14].

3. **Bitter Taste masking by Encapsulation:** When taste inhibition or mixture suppression fails to elicit the optimal taste there are other strategies that can be applied. Masking bitter taste through encapsulation can be an important solution for bitter herbs/drugs.

   Microencapsulation is a process of applying relatively thin coating to the bitter herb/drug particles The two main technologies available for microencapsulation are spray-drying of emulsions and coacervation.

   a. **Spray drying of emulsion containing bitter:** Spray drying is another cost effective techniques for the taste masking of bitters. The most common and widely used technique and then spray- dry the emulsion [15]. In this method, the mixtures of bitter and ingredients of emulsions are homogenized using high- speed homogenizer.

      The variables like mixture composition, time and intensity are optimized [16]. Later the homogenized emulsion is subjected to spray- drying using spray dryer where inlet gas temperature, outlet gas temperature, feed intensity and frequency of the atomizer disk rotation is monitored [17].

b. **Microencapsulation of Bitters using Coacervation technique:** The coacervation phase separation consists of three steps [18] – the first step involves the formation of three immiscible chemical phases comprised of solvent or vehicle phase, a coating material phase and the bitter herb/drug phase. The bitter herb/drug is dispersed in the coating material followed by the dispersion of this mixture into the solvent or liquid vehicle phase.

The coating material phase is different from the solvent or liquid vehicle phase so that either by changing the temperature or addition of electrolyte or by inducing polymer-polymer interaction, phase separation can be achieved. After applying the phase separation technique, in the step two, the polymer in liquid deposits on to the herb/drug particles. In the third and final step the rigidization of the coating material is done generally by thermal cross linking technique.

4. **Bitter Taste masking using other techniques:**

a. **Coating of Bitter Herbs:** Coating of particles is an important unit operation in the pharmaceutical industry. The coating of individual bitter particle with other smaller particles is commonly carried out to improve the taste characteristics of bitters. There are techniques to achieve this – wet particle coating and the dry particle coating. The dry particle coating is technology to coat particles without using organic solvent or water dispersion. In this method, relatively large particle size bitters are coated with fine particles (guest). The adhesion of these particles is made using mechano-chemical treatment or using plasticizer [19].

b. **Entrapping of Bitter herbs in inclusion complex forming agents:** The ring shaped excipient such as cyclodextrin bind certain bitter materials or flavors in their inside and and therefore stop them from being perceived by the senses of taste and odor.

β-Cyclodextrin is the most widely used complexing agent for inclusion type complexes. It is a sweet, nontoxic, cyclic oligosaccharide derived from starch. Cyclodextrin has a donought- shaped three-dimensional structure. Their inside is hydrophobic and their outside is hydrophilic. The inner cavity, therefore, attracts the hydrophilic molecules, and the hydrophilic exterior makes them suitable for formulations [20].

c. **Ion exchange resinate Bitter herbs complexes:** Complexes between ion exchange resins and drugs (known as resonates) have been used in pharmaceutical formulations for several decades. Ion exchange resins can be described quite simply as insoluble polyelectrolytes. They are insoluble polymers that contain ionizable groups distributed regularly along the polymer backbone.

Resinates being insoluble has no taste. This makes them excellent excipients for taste masking. However, this technology works well as long as rate of release of drug on contact with saliva is sufficiently slow. Use of resinate is particularly useful in liquid formulations. There are several examples of the use of this technology in the market place however, no literature on use of resinate with bitter herbs has been reported [21].

Methods to evaluate the effectiveness of taste masking of Bitter herbs: Taste is highly subjective property and hence it becomes limitation for measuring the effectiveness of taste masking method. The evaluation of taste is fundamentally different than evaluation of herb drug efficacy where therapeutic benefits are usually directly measurable. Literature survey reveals that there are two types of methods that are used to evaluate taste masking effectiveness. The first method is in vivo where human panels are used to rate the taste of the product. While in the second method, in vitro method, attempts are made to measure the parameters closely correlated to taste.

***In vivo* evaluation (to determine bitterness value):** The bitterness of herbs can be determined by the method described by WHO [2]. Or European Pharmacopoeia or mentioned elsewhere in the literature [23]. In this method, the herb bitter taste is compared as threshold bitter concentration (TBC) with the TBC of a dilute solution of quinine hydrochloride R. The bitterness value (units/g) is computed from equation as;

$$\text{Bitterness Value} = \frac{2000 \times C}{A \times B}$$

Where A = the concentration of the herbal stock solution in (mg/ml); B = the volume (in ml) of herbal solution with threshold bitter concentration, and C = the quantity of quinine hydrochloride R (in mg) with threshold bitter concentration.

The test is performed by human volunteer. For ethical reasons the human taste panel volunteers comprise of healthy human adults. As sensitivity varies from person to person, the same person should taste both the material within a short space of time. A certain amount of training is required to be given to the members of the taste panel. A person who does not feel the bitter taste after consuming 10 ml of solution of quinine hydrochloride R in 0.058 mg concentration is not include in the test panel for taste.

***In vitro* evaluation:**

Dissolution method: The problem of bitter taste is severe in liquid, chewables and fast dissolving preparations and objectionable taste leads to poor patient compliance. So far we have reviewed that there are two main techniques known in the art of masking the bitter taste of herbs/drug. The first is to add flavors or other material that can hide the objectionable taste. And the second is to limit the dissolution of the active substances in the saliva. Huges, [24] for the first time introduced the dissolution method for in vitro evaluation of taste masked preparation. The concept of this method is very simple. Incomplete dissolution of taste masked product is highly desirable property. The buccal residence time is usually short, few minutes, depending on saliva secretion rates. The undissolved components are removed from the mouth by swallowing and their residence time is of the order 5- 60 seconds.

In this method thus, the release medium used has composition similar to saliva and small volume of (5 ml).

The result of this method is that a transient dissolution curve can be generated whereby the peak concentration can be correlated with the taste intensity (time of experiment 2 minutes).

Electronic tongue method: The electronic taste sensing apparatus also called as e- tongue (ALPHA MOS, France) is being recommended for pharmaceutical use. The e- tongue has seven different sensors that are chemically modified field effect transistors. The e- tongue can recognize biological taste at three levels- the receptor level (taste buds in human probe membrane in 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) [25].

CONCLUSION: Taste masking concept is most important while formulating oral herb preparations when used especially for paedriatic and geriatric populations, who directly reject the bitter taste. Further the taste masking of bitter herbs can provide competitive advantage to manufacturing companies, particularly to the over the counter (OTC) products containing bitter herbs as the consumers will choose the brand that has overcome the bitter taste

ACKNOWLEDGEMENT: Authors are thankful to AICTE, New Delhi for funding this project.

REFERENCES:

1. Hutchins MO. Chapter 9: Chemical Senses: Olfaction and Gustation. [http://neuroscience.uth.tmc.edu/s2/ chapter 09.html].
2. Zhao GQ Zhang Y, Hoon MA, Chandrashekar J, Erlenbach I. The receptors for mammalian sweet and umami taste. Cell. 2003; 115: 255–266.
3. Eby GA. III Taste-Masked Zinc Acetate Compositions for Oral Absorption. US Patent 1992; 5: 095,035.
4. Katsuragi Y Sugiura Y Lee C, Otsuji K, Kurihara K. Selective inhibition of bitter taste of various drugs by lipoprotein. Pharm Res. 1995; 12(5):658-62.
5. Maehashi K Matano M Nonaka M, Udaka S, and Yamamoto Y. Chem. Senses. 2008; 33 (1): 57-63.
6. Stevenson RJ, Prescott J, Boakes R A. Confusing tastes and smells: how odours can influence the perception of sweet and sour tastes. Chem Senses. 1999; 24(6): 627-635.

7. Keast RS, Breslin PS. Bitterness suppression with zinc sulfate and na-cyclamate: A model of combined peripheral and central neural approaches to flavor modification. Pharm Res. 2005; 22(11):1970-7.
8. Mukherji, Gour, Goel, Sandhya, Arora, Vinod Kumar. Taste masked compositions United States Patent 6565877, 2003.
9. Fuisz R C. Taste masked medicated pharmaceutical**.** United States Patent 5028632.
10. Fu Y, Yang S, Jeong SH, Park K. Orally Fast Disintegrating Tablets: Developments, Technologies, Taste-Masking and Clinical Studies Critical Reviews™ in Therapeutic Drug Carrier Systems. 2004; 21(6):433–475.
11. Gowthamarajan K, Kulkarni GT, Narendra K. Pop the Pills without Bitterness Taste-Masking Technologies for Bitter Drugs. Resonance. December 2004; 25-32.
12. Ghebre-Sellassie, Ed., "Pharmaceutical Pelletization Technology", Drugs and the Pharmaceutical Sciences, vol. 37: 50-54.
13. Maniruzzaman M, Boateng JS, Bonnefille M, Aranyos A, Mitchell JC, Douroumis D. Taste masking of paracetamol by hot-meltextrusion: An *in vitro* and *in vivo* evaluation. European Journal of Pharmaceutics and Biopharmaceutics 2012; 80(2): 433–442.
14. Schaefer T, Holm P, Kristensen HG. Melt granulation in a laboratory scale high shear mixer. Drug Develop Ind Pharm 1990; 16: 1249-1277.
15. Liu XD, Atarashi T, Furuta T, Yoshii H, Aishima S, Ohkawara M. Microencapsulation of emulsified hydrophobic flavors by spray drying. Drying Technology 2001; 19, 1361–1374.
16. Adamiec J, Marciniak E. Microencapsulation of oil/matrix/water system during spray drying process. *Drying 2004* – Proceedings of the 14th International Drying Symposium (IDS 2004) São Paulo, Brazil, 22-25 August 2004, vol. C, 2043-2050.
17. Oneda F, Re MI. The effect of formulation variables on the dissolution and physical properties of spray-dried microspheres containing organic salts. Powder Technology 2003; 130 (1)377-384).
18. O'Donell PB, McGinity JW. Preparation of microspheres by the solvent evaporation technique. Adv Drug Del Rev 1997; 28:25-42.
19. Yang J, Sliva A, Banerjee A, Dave RN, Pfeffer R. Dry particle coating for improving the flowability of cohesive powders, Powder Technology, Special Issue in Memory of Prof. Molerus 2005; 158(1-3): 21-33.
20. Challa R, Ahuja A, Ali J, Khar R. Cyclodextrins in Drug Delivery: An Updated Review. AAPS PharmSciTech 2005; 06(02): 329- 357.
21. Irwin WJ, McHale R, Watts PJ, Drug Development and Industrial Pharmacy 1990; 16(6): 883–898.
22. Quality Control Methods for Medicinal Plant Materials. WHO, Geneva; 1998. 128. http://aps.who.int/ medicine docs/collect/medicinedocs/pdf/h1791e.pdf. Accessed 2009 Oct 2.
23. European Pharmacopoeia 5.0, Chapter 2.8.15, 2002; 221.
24. Huges L. Buccal dissolution of active substances. US Patent 7470545, 2008.
25. Zheng JY, Keeney MP. Taste masking analysis in pharmaceutical formulation development using an electronic tongue. International Journal of Pharmaceutics 2006; 310(1-2):118-24.

How to cite this article:
Kale V, Tapre C and Ittadwar A: Gustatory system and masking the taste of Bitter Herbs. *Int J Pharm Sci Res* 2013; 4(11): 4118-24. doi: 10.13040/IJPSR. 0975-8232.4(11).4118-24