TASTE ASSESSMENT TRIALS FOR SENSORY ANALYSIS OF ORAL PHARMACEUTICAL PRODUCTS

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ABSTRACT

Taste assessment trials are conducted with an aim to evaluate taste of tastants (food, chemical, drug etc.) and involve estimation of gustatory sensation responses in healthy human volunteers within well controlled procedures. Taste assessment trials are the standard and so far preferred method of taste assessment. Several in vitro taste assessment approaches have emerged as subsidiary methods but none could replace Taste assessment trials. The article provides an overview on conduct of taste assessment trials in healthy adult human volunteers and children.

Keywords: Taste assessment; taste panel; sensory analysis, taste masking, palatability.

INTRODUCTION

Taste of drug and drug product is an important parameter as it directly relates to the patient acceptability, compliance, and prescribing practice of various oral formulations (Nunn and Williams, 2005). Masking of unwanted taste provides commercial gains to pharmaceutical industries due to higher market demand of products, patent protection to novel taste masked formulations and also in some cases extended marketing exclusivity rights. The bitterness of drug or drug product is minimized or eliminated by various physical, chemical and physiological means. Taste assessment plays a pivotal role in characterization of novel taste masked pharmaceutical formulations. Assessment procedure typically involves three characteristics to be measured: taste quality (an important contributor to flavor), taste intensity (potency), and perceived intensity measured overtime (temporal profile). Thus, the overall taste perception reflects initial taste, aftertaste, flavor, and texture of the formulations. To date, however, most widely used and standard method for measuring these characteristics is psychophysical evaluation by taste panel. Although conventional chemical analyses based on release studies are subsidiary methods. As a recent topic, it has been reported that *in vitro* taste assessment approaches and BMTSS have been continuously decreasing the need to conduct Taste assessment trials (Anand *et al.*, 2007). However, these new approaches still are dependent on Taste assessment trials for validation purpose. Various approaches for taste assessment may be classified into three groups physiological approaches, in vitro studies and biomimetic taste sensing systems (BMTSS). Most of the Taste assessment trials are performed in adult volunteers even for commercially available formulations meant for children. Taste for drug and drug products are rarely studied in children due to stringent regulations due to safety reasons. Overall resulting effect is lack of suitable dosage forms for use in infants and young children (Nahata, 1999).

Taste assessment trials

Taste assessment trials are conventional physiological or psychophysical evaluation of tastants (food, chemical, drugs etc.) involving estimation of gustatory sensation responses in healthy human volunteers within well controlled procedures (Anand and Garg, 2001). Therefore, such studies are also called as physiological evaluation, psychophysical evaluation, gustatory sensation tests, sensory tests or taste panel studies. These are sensitive and built around a statistical design to minimize bias and variable responses within and between human volunteers. These can be used for assessing formulation and ingredient impact and intensity so that full profiles can be produced. These, in turn, can be statistically related to patient attitudes and expectations and give a precise guide to formulation development that will meet the patient needs. Role of taste assessment trials and taste assessment in the oral drug product development has been shown in fig. 1. Hence, Taste assessment trials are essential part of clinical oral drug product development and quality control of oral drug products which are adapted to the need of special populations' *viz.* pediatrics, geriatrics, patients suffering from psychological diseases, persons having swallowing disorders.

Stimulus, test or standard, is applied on the tongue of the healthy human volunteers. Biological membrane of taste buds on the tongue receives the stimulus and transmits

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this information as electric signal, which is further transmitted along the nerve fiber to the brain where the taste is perceived.

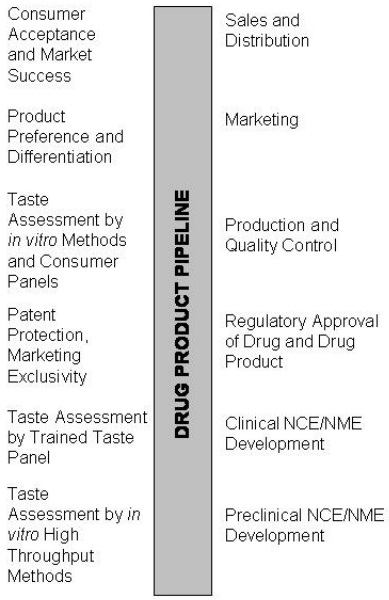

Fig. 1: Importance of taste assessment trials in drug.

Approval of trial by IRB/IEC

Trial protocol is first prepared and submitted to Institutional Review Board (IRB) or Institutional Ethical Committee (IEC). Relevant components of the protocol are presented in Box 1. IRB/IEC shall be constituted according to Good Clinical Practice (GCP) guidelines. These guidelines have been evolved by different regulatory agencies like World Health Organization (WHO), International Conference on Harmonization (ICH), United States Food and Drug Administration (USFDA), European GCP, Schedule Y of Drugs and Cosmetics Act 1940 (Indian Act), or Indian Council for Medical Research (ICMR) or other clinical trials regulatory agencies. IRB/IEC, comprises of medical/ scientific and non-medical/non-scientific members, is pivotal in starting clinical trials, Taste assessment trials of drug products and other studies involving human subjects (Anand *et al.*, 2006). IRB/IEC has responsibility to verify the protection of the rights, safety and well-being of human subjects involved in study. The independent review provides public reassurance by objectively, independently and impartially reviewing and approving the "Protocol", the suitability of the investigator(s), facilities, methods and material to be used for obtaining and documenting "Informed Consent" of the study subjects and adequacy of confidentiality safeguards. Research activities that present no more than minimal risk to human subjects may be reviewed and approved by IRB/IEC in one of its convened meeting (Choudhury *et al.*, 2005).

Selection of human volunteers

Human volunteers are identified and screened for inclusion and exclusion parameters of the study *viz.* age, health, use of other medication, consumption of alcohol, pregnancy, smoking behavior, allergy, impaired stimulation/perception towards taste, dental hygiene etc.. Volunteers are informed about the study procedure, toxicity of drug or formulation and risks involved. Thereafter, informed consent is obtained on an IRB/IEC approved form. Volunteer details (name, age, sex or other information) are kept confidential and provided only to IRB/IEC or committees which work in the protection of rights of human subjects. Volunteers have to refrain themselves from eating, drinking or chewing gum for at least an hour before testing.

Training to human volunteers

Human volunteers are trained to understand the correct way of conducting the taste assessment without considering their personal preferences. Training session includes the activities like sample application method, tasting of sample, intensity rating, use of appropriate scale and expectoration of samples. Volunteers assess the taste quality, intensity and in some cases temporal profile of samples. The correct use of scale should be emphasized to each an every human volunteer.

Human volunteers shall pass basic sensory training tests for becoming member of product panel team. Panel members are tested for their ability to taste and to express sensory perceptions. Successively they receive product-specific training before joining a product panel team. The performance of the sensory analysis panel members is validated regularly. Following the validation, the performance of each individual panel member is evaluated and presented to him/her.

Standard stimuli

Highly pure chemicals or drugs and deionized water are employed in preparation of standard solutions for stimulus application. Freshly prepared solutions are utilized for taste assessment but if storage of solution is required they should be kept at 4-8°C in amber glass bottles. Stored solutions should bring up to room temperature prior to testing with the aid of a water bath. Deionized water is used as the blank stimulus and the rinsing agent.

Stimulus application and tasting

Volunteers rinse and expectorate with deionized water several times prior to testing for neutralization of previous tastes. Small (2-5 ml) amount of drug solution or drug or drug in powder or granules or drug product unit dose, standard or test, is dispensed using disposable pipettes or

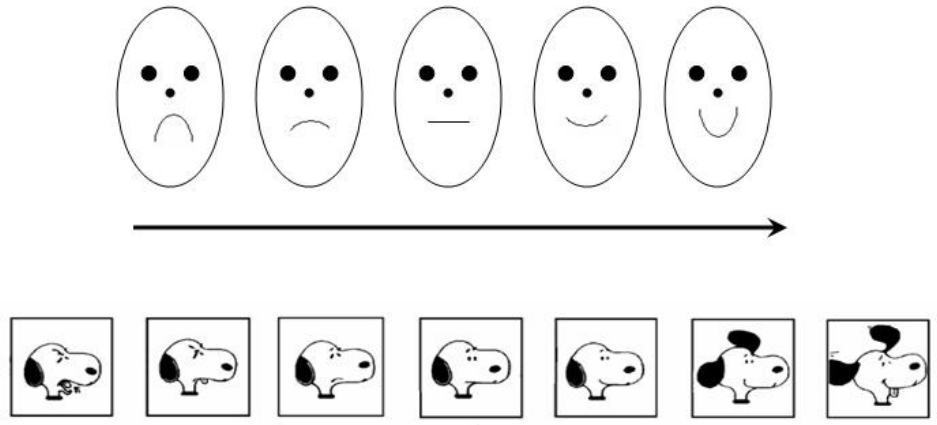

Fig. 2: Hedonic scale for measurement of taste.

Table 1: Sensory scales for measurement of taste intensity

Scale	Features	Examples
Nominal Scale	Labeling without any ranking	Numbers on shirts of soccer players
Ordinal Scale	Provide rankings but lack in defining size of interval between the numbers	Category scales such as 1= very weak, 5= medium, 9= very strong
Interval Scale	Provide information about size of intervals to be ranked	Measurement of time as dates on calendar
Ratio Scale	Rank so that the scale has ratio properties i.e. a stimulus rated at 50 is twice as intense as one at 25	Measurement of length in inches

sipped from test tubes or medicine cups or placed on the tongue by scooping. In some of the studies impregnated filter paper, cut in the shape of tongue, has been placed on the tongue of volunteers. Volunteers taste the applied sample by holding it for an appropriate time in the mouth, rate taste qualities and intensity and then rinse mouth thoroughly with deionized water after each tasting. All samples are presented in random order with an appropriate inter-stimulus interval. Salty crackers and water are provided to neutralize taste after tasting standard or test sample. Taste evaluation is for next sample starts only after proper neutralization of taste due to previous stimulus. If necessary, subjects wore nose-clips to eliminate olfactory input while rating.

For estimation of bitterness intensity standard solutions of quinine hydrochloride, caffeine (Salazar de Saavedra and Saavedra, 2000) may be used. Some recent studies utilizes standard quinine hydrochloride concentrations of 0.01, 0.03, 0.10, 0.30, and 1.00 mM and the corresponding bitterness scores defined as 0, 1, 2, 3, and 4, respectively (Ishizaka *et al.*, 2004, Nakamura *et al.*, 2003, Ogawa *et al.*, 2004, Uchida *et al.*, 2001). Multiple ratings for intensity may be averaged to yield single rating of bitterness (Breslin and Beauchamp, 1995; Keast *et al.*, 2003). The bitter properties of plant material are determined by comparing the threshold bitter concentration of an extract of the material with that of a dilute solution of quinine hydrochloride (WHO, 2002).

Sensory analysis of oral pharmaceutical products

Sensory evaluation by psychophysical means requires human volunteers which shall take part in sensory test. Such group of assessors selected to take part in a sensory test is called panel and individual assessor participating in the sensory test in known as panelist. Clearly defined objective of any sensory or taste evaluation is fundamental part as it will determine the type and age of subjects and the methodology to design, conduct and interpret the study and its outcome (Gillette, 1990). In oral drug product development stages of pharmaceutical industry, oral drug products are tested by sensory panels

to determine chosen set of variants which are the preferred and the ideal candidate for further consumer testing leading to commercialization. Thus sensory panels are the industry's standard in oral drug product development as they provide indication of important attributes to the taste, aroma and texture of a drug product. Mapping the sensory panel descriptions and linking this data with consumer tests provides key elements that drive preference which can be optimized to cater the need of consumers and this technique is used to identify taste segmentation groups.

Evaluation principles

Taste assessment trials are designed in a manner to evaluate parameters like taste, aftertaste, flavor, aroma, texture and mouthfeel. Questions for asking the individual perception for the adjectives are kept simple, and intelligible. Ideally, the asked questions should be independent of the age, social and developmental level of the volunteers. Simple language and commonly used terms relevant to the age of volunteer are highly recommended to describe the properties of taste characteristics, aftertaste, flavor, texture and mouthfeel.

- Taste Characteristics: sweet, salty, sour, and bitter
- Aftertaste: Bitter, sweet, salty, sour, umami, astringent, numbness, or freshness
- Flavor and aroma:
- Texture and mouthfeel: thin, thick, viscous, gritty

Testing of abovementioned parameters could be effected by discrimination tests, scaling tests, expert tasters, affective tests and descriptive methods (Worlington, 2001).

Discrimination tests

These tests are used to distinguish differences among products and may be carried out either by performing difference test or ranking. *Difference test* tell if there are perceivable differences between products by analyzing qualitatively or quantitatively especially when product differences are small. These tests may be used for quality control, cost control and ingredient substitutions. Difference tests are easy to conduct and the statistical data treatment is fairly simple. *Ranking test* simply ranks a series of samples in order for a specific characteristic, such as bitterness or flavor. Preliminary screening of products may be achieved with ranking tests. However, the study results may be biased due to limited memory and attention of the taster during the entire testing period. This limitation may be more pronounced depending on the age of the subjects participating.

Scaling tests or scoring

The test uses a score sheet to collect information on specific product attributes such as flavor and industries for quality physical appearance for product grading. Such tests are used in meant and dairy industry for quality.

Expert tasters

An expert is a formally qualified assessor who possesses specialist technical knowledge and experience and who is responsible for testing particular products/product groups. One or more experts in a category evaluate qualitative and quantitative measures. Expert tasters are used mainly in the wine, coffee, beer, and tea industries to "craft" measures the products.

Affective or hedonic testing

Affective or hedonic testing is used to evaluate the popularity of an aroma and/or taste impression according to like/dislike. Samples are presented in succession and the subject is told to decide how much one like or dislike the product and to mark the scales accordingly. The nature of this test is its relative simplicity. The instructions to the panelist are restricted to procedures, and no attempt is made at direct response. The subject is allowed, however to make their own inferences about the meaning of the scale categories and determine for themselves how they will apply them to the samples. A separate scale is provided for each sample in a test session. Different consumer panels are employed in studies for characterizing attributes such as suitability, image and preference.

Affective testing includes paired tests, acceptance tests and just about right tests. *Paired tests or Multiple paired comparison tests* measure the response to two or more products respectively for preference to an attribute, e.g. bitterness of products. The test involves marking of the product that is most or least bitter. Multiple paired comparison tests involve a number sample pairs. *Acceptance test* are employed to measure the degree of like or dislike of a product or specific attribute, for example, 9-point scale ranging from "like extremely" to "dislike extremely". Acceptance tests are mostly and frequently used by market research and R&D to ascertain consumer response to products. *Just about right* determines the appropriateness of a right specific attribute, such as level of bitterness or sweetness.

Descriptive methods

Descriptive testing is used to describe the total sensory picture of a product. Differences in product attributes are described in words and numbers by rating sensory attributes, covering appearance, texture, taste and odor. These methods are most useful for process development, quality assurance, trouble-shooting, benchmarking and guiding product development in food and pharmaceutical industries.

Scales of intensity

Volunteers assess taste quality and intensity on different adjective scales. Adjective scales includes various parameters of sample such as overall intensity, sweet, sour, salty, bitter, metallic, cooling, hot, spicy, burning,

anesthetic, astringent, medicinal, minty/menthol, warming, sharp, alcohol, painful, irritating, stinging, dry, peppery, and paper (Schiffman *et al.*, 2000). Each adjective may be rated on intensity scale ranging from 0 (none at al) to four or up to nine point (highest point on scale give maximum intensity) on provided score sheets. While studying temporal profile**,** the intensity of adjectives is determined at different time points (e.g. bitterness intensity instantly and then after 10 sec, 1, 2, 5 and 15 minutes). Such type of assessment is also known as time intensity method of estimating adjective (Avari and Bhalekar, 2004; Borodkin and Sundberg 1971; Lugaz *et al.*, 2005; Salazar de Saavedra and Saavedra, 2000).

Taste may be compared across individuals using labeled category scales. Initially investigators assumed that adjectives like weak and strong referred to the same sensory intensities for all subjects. However, the use of adjective scale has decreased with time as adjectives like weak and strong in different subjects do not convey the same meaning. SS Steven, a Harvard Psychologist, classified sensory scales (table 2) of measurement into four different types (Barthoshuk, 2000) *viz.* nominal scales, ordinal scales, interval scales and ratio scales.

In magnitude estimation of intensities, subjects are asked to assign numbers to perceived intensities such that one stimulus is twice as intense as another is assigned a number twice as large. The numbers on this scale thus have ratio properties. However, magnitude estimates cannot be compared across subjects because we cannot share one another's experience. Steven's sensation scales measure relative intensities only within a subject, not across subjects.

Labeled magnitude scale

It has intensity adjectives spaced so that the scale would have ratio properties (i.e. a stimulus rated at 50 is twice as intense as one at 25) and hence it can be used in place of magnitude estimation. Green and his associates developed such a scale which is named after him i.e. Green Scale (Green *et al.*, 1996; Green *et al.*, 1993). The upper extreme of scale is the strongest imaginable taste. The scale does not reflect perceived intensities across individuals and thus could not be used for magnitude matching across individuals. However, such scale e.g. Green's scale, have provided insights about the severity of ceiling effects in psychophysical studies which may conceal variations in perceived intensity (Barthoshuk, 2000).

Equivalent density examination method

Subjects compare the taste intensity of a test solution with that of the standard solutions and select the standard solution having a taste equivalent to that of the given test solution (Ishizaka *et al.*, 2004; Katsuragi *et al.*, 1997).

Pharmaceutical formulation considerations

Enough care should be taken when pharmaceutical formulations are evaluated for taste or palatability. Odor may interact with taste and hence in some of the studies, when evaluating odor and taste separately, nose-clips should be applied to human volunteers during tasting of samples. With the nature of pharmaceutical dosage form, test stimulus application will differ. Liquid oral formulations, viz. suspensions, emulsions, solutions, elixirs etc., may be presented in test tubes (Katsuragi *et al.*, 1995) or medicine cups or with the help of pipettes (Fergonezi-Nery *et al.*, 2002). Granules, microspheres, powders may be directly placed on tongue and compared its bitterness intensity with that of the standard quinine solution (Katsuragi *et al.*, 1997) or pure drug or placebo (Anand and Garg, 2001; Nanda, 2000). Dry syrups are suspended in the prescribed vehicle for making test sample. Fast disintegrating or dissolving tablets may be evaluated for taste by directly placing them on tongue and allowed for complete disintegration/dissolution followed by bitterness intensity rating (Dandagi *et al.*, 2005). Summary of several taste assessment trials have been provided in table 2. A physical model approach to taste studies of drugs and pharmaceutical formulations has been developed which consist of porous half diffusion cell placed on the surface of an extended human tongue and the recording of the times for psychophysical taste response provide quantification and mechanistic understanding of the taste of drugs and physical formulation factors (Ho, 1984).

Taste assessment in children

Children are regarded as the most suitable panel for taste assessment of pediatric formulations as these are ultimate target population for most of the taste masked drugs or formulation. Only 20 percent to 30 percent of drugs approved by the Food and Drug Administration are labeled for pediatric use (Meadows, 2003) due to ethical/moral issues, difficulties in attracting pediatric patients into studies, difficult administration, compliance issues and little revenues and substantial product liabilities. Furthermore, taste assessment studies in children lack adequate description in the regulatory guidances. Due to involvement of human testing these are regarded as clinical studies which must be performed by duly qualified personnel with IRB or IEC approval. Designing suitable safe studies in which children can easily participate is really a difficult task due to ethical requirements for appropriate informed consent from parents or guardians and assent from the child. Adults can give informed consent to participate in a clinical trial, children can't because "consent" implies full understanding of potential risks and other considerations. Children ages 7 or older can "assent" or "dissent," meaning they can agree or disagree to participate in a study. Therefore, informed consent is generally obtained from parents or guardians and assent from children.

Table 2: Summary of several taste assessment trials

Study	Subjects and Study Plan	Standard Stimuli	Test Stimuli	Sample Delivery Method	Taste Neutralization and Interstimulus Interval	Scale of Measurement	Reference
Suppression of bitterness by sodium.	Subjects Number: 12-27; Age 21 to 30	Standard solutions prepared in de-ionized water. Urea, caffeine, quinine HCl, amiloride were used as bitterness standards	Bitter salt mixture series (containing only one salt and one bitter agent), each solution (n=12 or n=16) was sampled twice	All samples were delivered in 10 ml volumes in polystyrene medicine cups	After tasting subjects were required to rinse twice thoroughly with deionized water during the approximate 60 s interstimulus interval.	Intensity matching method was adopted with 0.1 and 1.0 mM QHCl as medium and high levels of bitter sensation	Breslin and Beauchamp, 1995
Selective Inhibition of bitterness by phospholipids.	5 to 8 paid volunteers	Standard quinine sulfate, sucrose, sodium chloride, tartaric acid known concentrations for values on intensity scale from 1 to 10	Solutions of sucrose, sodium chloride, tartaric acid, quinine sulfate with added phospholipids (Phospatidic acid, phosphatidylethanol-amine, phospatidylinositol, phosphatidylcholine) and granules quinine + phosholipids granules	Test and standard solutions: About 5 ml of each solution was added to a separate test tube placed on the tongue. Granules: 100 mg were placed on the tongue till granules were completely dissol-ved on the tongue	Rinsing of mouth thoroughly with deionized water	10 point bitterness intensity scale	Katsuragi *et al*, 1997
Inhibition of bitter taste of Polymyxin B Sulfate and Trimethoprim Sulfamethoxaz ole by BMI-60.	Children in age group 3 to 6 = 5; Children in Age Group 8 to 16 = 4 Total nine children. Adult Volunteers: Five	Quinine sulfate solution at different bitterness intensities (1 to 10)	Dissolving one polymyxin B sulfate, one bactramin (sulfametho-xazole + trimethoprim) tablet and one polymyxin B sulfate plus one bactramin tablet in 10 ml of deionized water. Effect of addition of BMI 60 from 0.05 to 1 g was evaluated.	Teaspoonful of solution placed on the tongue	Rinsing of mouth thoroughly with deionized water.	10 point bitterness intensity scale	Saito *et al*, 1999
Palatability and cost comparison of five liquid corticosteroid formulations	Double blind palatability test (taste, aftertaste, texture and overall accep-tance) of five liquid corticos-teroid formula-	No standard bitterness solution. Only five test formulations were used.	Taste masked commercial formulations Pediapred , Prelone, prednisone oral solution and prednisone l0-mg tablet crushed in 10 ml of cherry syrup	A few drops of formulation was placed on the spoon and administered at home by the family members to patients	Five point scale (least palatable to most palatable). Subjective responses like significant facial expressions, comments, behavior etc.		Hutto *et al*, 1999

Study	Subjects and Study Plan	Standard Stimuli	Test Stimuli	Sample Delivery Method	Taste Neutralization and Interstimulus Interval	Scale of Measurement	Reference
	tions. Seven members of the nursing research group conducted study in children						
Taste masking as a consequence of organization of powder mixes	A single blind taste test was used for the taste-mask-ing evaluation. A panel of 10 healthy volunteers: six females and four males with ages ranging from 18 to 40 and weights ranging from 47 to 80 kg participated to this study and gave their informed consent.	Pure excipient and pure active ingredient was also given apart from drug excipient mixtures. Powders were placed on microscope slides. The volunteers were asked to taste the powders by sampling them directly with their tongue.	Binary mixtures of drug with excipients (nifulmic acid, Ibuprofen; Excipient, ethylcellulose, HPMC, with	each volunteer tasted five powders at least 2 h after lunch or coffee for 4 days	Five powders were tasted 2 hr after lunch or coffee for four days	Taste evaluation began immediately after administration and continued for up to 30 s. The scale used a ranking system from 0_tasteless.to 3_very irritating or very bitter.	Barra *et al*, 1999
Palatability of oral antibiotics effective in the therapy of otitis media in healthy pediatric volunteers	Single-blind, multicenter, randomized, comparative taste test for 4 antimicrobial suspensions was conducted at 3 primary care pediatric centers and involved a volunteer sample of 90 healthy children (5 to 9 years of age).	Only test samples of 2.5 ml each antimicrobial suspension was given to patients	Azithromycin (cherry flavored), cefprozil (bubble gum flavored), cefixime (strawberry flavored), and amoxicillin/clavulanate (banana flavored).	The antimicrobial agents were presented in a balanced, randomized order as determined by arrangement in a Latin square.	Cracker to eat and rinse and swallow water	10-cm VAS visual analog scale (VAS)	Toscani *et al*, 2000
Sensorial response model to the design of	Three trained individuals	Standard caffeine solutions		1 ml sample swallowed and readings were taken	Washout period with distilled water	Analog scale associated with standard	Salazar de Saavedra, 2000

Study	Subjects and Study Plan	Standard Stimuli	Test Stimuli	Sample Delivery Method	Taste Neutralization and Interstimulus Interval	Scale of Measurement	Reference
an oral liquid pharmaceutical dosage form				immediately and at 12 intervals of 15 s over a period of 3 minute		caffeine solutions	
A taste study of several antibiotic suspensions	This randomized, single-blind, paired-comparison crossover study	Amoxicilin antibiotic suspension was used as positive	Cefuroxime axetil suspension (125 mg/5 ml or 250 mg/5 ml) with that of 3 other antibiotic	They were then administered in counterbalanced order 2.5 ml of 2	2-3 minute washout period; palate cleansing with soda cracker and water	5-point facial hedonic scale (from 1 = really bad to 5 = really	Schwartz *et al*, 2000
	was conducted to compare the taste of cefuroxime axetil suspension. Two hundred children aged 3 to 8 years received cefuroxime axetil and 1 of 4 other treatments in counterbalanced order.	control with which palatability of other antibiotics were compared	suspensions (cefpodoxime proxetil 100 mg/5 ml, clarithromycin 250 mg/5 ml, and amoxicillin 250 mg/5 ml) and chocolate syrup added to formulations.	suspensions and were asked to rate the immediate taste (directly after dosing) and the aftertaste (60 seconds after dosing) of each medicine.		good). Questions asked to parents regarding children reaction	
Taste Test: Children rate flavoring agents used with activated charcoal	Double blind study randomized Healthy volunteers age 3 and 17 in prospective masked trial; Subject tasted 5 substances in random order		Activated charcoal without and with coca cola, cherry flavored syrup, chocolate milk and sorbitol	5 ml of test samples were sipped once	water in between more samples	Less than 8 year used 10 point facial hedonic scale; Over 8 years used 100 point visual analog scale	Skokan *et al*, 2001
Sensory evaluation of albendazole suspensions	n=24 trained judges in individual cabins; Sensory analysis repeated twice in completely randomized blocks. Blinding control		Three formulations of albendazole suspension	Holding the sample for till complete impregnation of mouth and the time necessary to detect the difference	Residual taste removed by rinsing with water eating a piece of apple before testing the following sample.	10 point scale (0 to 9) from no difference to extremely different	Frigonezi-Nery, 2002

Study	Subjects and Study Plan	Standard Stimuli	Test Stimuli	Sample Delivery Method	Taste Neutralization and Interstimulus Interval	Scale of Measurement	Reference
A taste comparison of three liquid steroid preparations: prednisone, prednisolone and dexamethasone	18 to 50 yr old volunteer; 86 adult volunteer 53 male and 33 female		Commercial steroid preparations of Prednisone prednisolone sodium and dexamethasone	5 ml of steroid preparation; medication cups	saltine cracker and water	Five point scale	Mitchel *et al*. 2003
Effect of quinine solutions on intracellular Ca++ levels in	Healthy volunteers (nine women and men aged 20-23 years) were well informed and then	The volunteers were first asked to keep standard quinine hydrochloride solutions (0.01,	Quinine solutions of various concentrations	In volunteers mouths for 15 s standard and test samples	Gargle with water and 20 minute interstimulus interval	Equivalent density determination method	Nakamura *et al*, 2003
neuro 2a cells. Combination effect of L-arginine and NaCl on bitterness suppression of amino acid solutions	joined the gustatory sensation tests	0.03, 0.1, 0.3, 1,3 mmol/l)					
Palatability of oral antibiotics among children in an urban primary care centre	30 Healthy children (5-8 years), Randomized single blind taste test to determine palatability of four antimicrobial agents	Only test solutions of antimicrobial suspensions were used in the study.	Azithromyein (cherry flavored), cefprozil (bubble gum flavored), cefixime (strawberry flavored), and amoxicillin/clavulanate (banana flavored).	2.5 ml of the antimicrobial suspension was given in plastic medication cups by research nurse or principal investigator	Cracker to eat and rinse mouth with water and swallow to remove residual taste	10 cm VAS incorporating a facial hedonic scale	Angelli *et al*, 2004
The combination effect of L-arginine and NaCl on bitterness suppression of amino acid solutions	Six adult volunteers	Standard Quinine hydrochloride concentrations 0.01, 0.03, 0.10, 0.30 with corresponding bitterness scores 0, 1, 2, 3, and 4, respectively.	Test chemicals were sweeteners (sucrose, aspartame), NaCl, various acidic (L-aspartic acid, L-glutamic acid), or basic (L-histidine, L-lysine and L-arginine) amino acids, tannic acid and phosphatidic acid	Scooping 2-5 ml of standard or test solution on the tongue and granules on the tongue. All samples were kept in the mouth for 15 s.	Rinsing of mouth thoroughly with deionized water and interstimulus interval of 20 minutes.	Intensity scale 1 to 4 (Equivalent density examination method)	Ogawa *et al*, 2004

Study	Subjects and Study Plan	Standard Stimuli	Test Stimuli	Sample Delivery Method	Taste Neutralization and Interstimulus Interval	Scale of Measurement	Reference
Evaluation of bitterness intensity of commercial taste masked clarithromycin dry syrup (Taginake *et al*, 2003) Evaluate the bitterness of 18 different antibiotic and antiviral formulations for pediatrics (Ishizaka *et al, 2004).*; Bitterness suppression of macrolide dry syrups by jellies (Tsuji *et al*, 2006)	5 to 9 healthy adult volunteers n==9 (Taginake *et al*, 2003), n=7 (Ishizaka *et al*, 2004)) n= 5 or 6 (Tsuji *et al*, 2006)	Standard Quinine hydrochloride concentrations 0.01, 0.03, 0.10, 0.30 with corresponding bitterness scores 0, 1, 2, 3, and 4, respectively.	Taste masked formulations	Scooping 2-5 ml of standard or test solution on the tongue and granules on the tongue. All samples were kept in the mouth for 15 s.	Rinsing of mouth thoroughly with deionized water and interstimulus interval of 20 minutes	Intensity scale 1 to 4 (Equivalent density examination method)	Tagninake *et al*, 2003; Ishizaka, 2004; Tsuji *et al*, 2006
Rapidly disintegrating risperidone summary of phase I clinical trials assessing taste, table disintegrating time, bioequivalence and tolerability	Four open label, Randomized Crossover trials; 1 was pilot trials, and all of the trials were short-term. Age of subjects 18 to 65 years and physically healthy (volunteers) or had a diagnosis of schizophrenia of any subtype or schizoaffective disorder.		Rapidly disintegrating and conventional risperidone tab lets.	RDT placed on tongue till it disintegrates completely and held in the mouth for appropriate time to assess the taste.	Coffee, tea, soft drink, a piece of cake after administration of RDT	5-step scale (1 = "very nice/pleasant"; 2 = "nice/pleasant"; 3 = "neutral"; 4 = "bad"; and 5 = "very bad") for measuring intensity of taste.	Thyssen *et al*, 2007

Box 1: Protocol development considerations.

COMPONENTS OF PROTOCOL FOR TASTE TRIALS
General Information: Study Background, Safety Information and Rationale
Objectives and Justification
Ethical Considerations: Declaration of Helsinki
Study design
Study Materials: Pharmaceutical Product and Handling of the Product(s), Test Amount=Less Than One Daily Doses for Youngest Child in the Study
Study Procedures
Study Population: Approximate number of subjects, Inclusion, Exclusion, Withdrawal and Termination of Subjects, Selection of Special Groups as Research Subjects, Subjects in Good Health, No History of Allergic Reactions to Any Ingredient of the Test Products, No Medication at the Time or 48 hours Preceding the Study
Assessment of Efficacy and Safety
Statistics
Data handling and management
Quality control and quality assurance
Finance and Insurance
Publication policy
Evaluation
Statement of Research
Ethics Committee and Protocol Approval Process
Informed Consent Process, Voluntary Participation Statement and Parallel and Child Consent
Confidentiality Prospective Research Subjects and Confidentiality of Records
Benefit to Subjects
Adverse Events and Reasonable Unforeseeable Risks
Compensation for Participation and Accidental Injury
Applicable GLP, GMP and GCP Guidelines
New Findings and Further Studies

Age of 4 years or older is generally considered suitable to participate in taste assessment panels. Children less than 4 years are difficult to recruit due to shyness and their reluctance to such studies. Further limitations of children less than 4 years include limited ability to understand and follow the guidance; lack of interest, difficulty in concentrating during the study period, inadequate communication of feeling and preferences (Bagger-Sjbȯck and Bondesson, 1989; Samulak *et al.*, 1996). It is highly recommended to start taste assessment with known compounds or at high concentrations of testing agent which may be followed with unknown or specific compounds. However this is not always possible to proceed in this manner due to very high intensity of compound with high concentration of testing agent. Residual taste may be removed by repeated rinsing of the mouth, eating of salty crackers and a sufficiently long interval between sessions. Verbal judgment and facial hedonic scales are the preferred doctrines for taste evaluation in palatability studies with children (Sjvall *et al.*, 1984).

Verbal judgment

Scoring of taste in a scale of e.g., 1 to 5 (score 1 corresponds to very good and score 5 to very bad) facilitates the statistical evaluation of the data obtained (Steele *et al.*, 2001). Children below 5-6 years are not considered to be able to express differences in taste perception by use of the preferential method. A reliable estimation of differences particularly in this age group (<5 years) might be achieved using the child's own spontaneous verbal judgments following a control question.

Facial hedonic scale

It allows the expression of preferences using a pictorial scale (fig. 2). The facial hedonic scale can not be used solely to discriminate between the tastes of tested formulations in the lowest age group. Sometimes young children may correlate the pictures with things other than taste thus it is used not as the sole method to assess taste in the lowest age groups. Facial expressions like wry faces and behavior pattern like shrug shoulders, vomiting and spitting the formulation out of mouth may also provide indication for the acceptance of formulations by the subjects (Bagger-Sjbȯck and Bondesson, 1989, Samulak *et al.*, 1996). Expressions of "noncompliance of drugs due to bitter or undesirable taste" and "compliance of drugs" may be used for studying effect of taste masking agents in the formulations (Saito *et al.*, 1999). Palatability and taste assessment studies can be further made more reliable and result oriented by involving parents, guardians or health providers in the study, asking about any discomfort or other observations in relation to the acceptance of the study medication.

Pros and cons of taste assessment trials

Taste assessment trials are extremely helpful to manufacturers, formulation scientists and food technologists to get a clear perception of consumers towards the product. When compared with most of the non sensory methods, it is rapid. Use of more than one sense is added advantage in comparison of products on the basis of multiple qualities. Taste assessment trials are most sensitive and excellent in detecting minute differences in product characteristics. The information obtained from trials may be utilized for writing specifications for quality. Lease laboratory facilities are required to conduct descriptive analysis of products.

Time consuming nature, requirement of major capital investments, extensive training of personnel and

difficulties in data analysis, and interpretation are major limitations of Taste assessment trials. Furthermore, the methodology is not amenable to screening very large numbers of samples rapidly and economically. Human panels typically present several difficulties including health concerns, poor memory, fatigue of tasters, personal preferences, maintaining the motivation for tasting unpleasant compounds and the lack of analytical standardization. Some other variables like salivary mixing, mixture suppression and time resolution may also complicate the methodology. Toxicity of drugs, genetic variation in taste (Barthoshuk, 2000), individual perception in bitter taste (Green and Hayes, 2004), and age dependency on perception of bitter taste (Mojet *et al.*, 2003) limits the applicability of human taste panel studies. New drug molecules before Phase I of clinical trials cannot be ethically tasted by human beings. Even in early phases of product development use of taste panel for taste assessment is not appreciable either due to cost or safety issues.

CONCLUSIONS

With the advancement in taste modifying techniques in food and pharmaceutical industries, the importance of taste assessment is continuously increasing. Novel in-vitro taste assessment approaches, *viz. in vitro* assay, drug release studies and taste sensors, are coming up to replace taste assessment trials. Taste assessment trials are continuously evolving with much more emphasis given to the ethical concerns of participants. Attempts have been started to frame regulatory guidelines for taste assessment trials specifically in pediatric patients. Despite emerging in-vitro approaches, taste assessment trials are and will remain the standard, preferable and most reliable approach for taste assessment.

REFERENCES

Anand V and Garg S (2001). Development and evaluation of novel taste masked formulation of prednisolone. *M. S. (Pharm.) Thesis,* NIPER, S. A. S. Nagar, Punjab.

Anand V, Kataria M, Beniwal P, Kukkar V, Choudhury P and Juneja T (2006). Regulatory pathway to assess taste of medications: A determinant to patient compliance and acceptability. *Indian Pharmaceutical Association National Conventoin Community Pharmacy Division* 3rd and 4th February 2006, Pune, India.

Anand V, Saharan V, Kataria M, Kukkar V and Choudhury P (2007). The latest trends in the taste assessment of pharmaceuticals. *Drug Discov. Today,* **12**(5/6): 257-265.

Angelilli M, Toscani M, Matsui D and Rieder M (2000). Palatability of oral antibiotics among children in an urban primary care center. *Arch. Pediat. Adolesc. Med.,* **154**: 267-270.

Avari J and Bhalekar M (2004). Cation exchange resins for taste masking and rapid dissolution of sparfloxacin. *Indian Drugs,* **41**: 19-23.

Bagger-Sjbȍck D and Bondesson G (1989). Taste Evaluation and compliance of two pediatric formulations of phenoxymethylpenicillin in children. *Scan. J. Prim. Health Care,* **7**: 87-92.

Barra J, Lescure F and Doelker E (1999). Taste masking as a consequence of the organisation of powder mixes. *Pharm. Acta. Helv.,* **74**(1): 37-42.

Barthoshuk L (2000). Comparing sensory experiences across individuals: recent psychophysical advances illuminate genetic variation in taste perception. *Chem. Senses,* **25**: 447-460.

Borodkin S and Sundberg D (1971). Polycarboxylic acid ion exchange resin adsorbates for taste coverage in chewable tablets. *J. Pharm. Sci.* **60**: 609-623.

Breslin P and Beauchamp G (1995). Suppression of bitterness by sodium: variation among bitter taste stimuli. *Chem. Senses,* **20**: 609-623.

Choudhury P, Kukkar V, Anand V, Kataria M and Juneja T (2005). Institutional review board or institutional ethical committee: mentor to clinical research. *57th Indian Pharmaceutical Congress 2005* 2nd to 4th Dec.2005, Hyderabad, India.

Dandagi P, Sreenivas S, Manvi F, Patil M, Mastiolmath V and Gadad A (2005). Taste masked ofloxacin mouth disintegrating tablets. *Indian Drugs,* **42**(1): 52-55.

Fergonezi-Nery M, Prudencio-Ferreira S, Kedor E, Baracat M and Brinholi F (2002). Sensory evaluation of albendazole supensions. *Brazilian Arch. Biol. Tech.,* **46**(4): 457-463.

Gillette M (1990). Sensory evaluation: analytical and affective testing. *Perfumer & Flavorist,* **15**: 33-40.

Green B, Dalton P, Cowart B, Rankin K and Higgins J (1996). Evaluating the labeled magnitude scale for measuring sensation of taste and smell. *Chem. Senses,* **21**: 323-334.

Green B and Hayes J (2004). Individual differences in perception of bitterness from capsaicin, piperine and zingerone. *Chem. Senses,* **29**: 53–60.

Green B, Shaffer G and Gilmore M (1993). A semantically labeled magnitude scale of oral sensation with apparent ratio properties. *Chem. Senses,* **18**: 683-702.

Ho N (1984). Physical model approach to taste studies of drugs and pharmaceutical formulations. *J. Pharm. Sci.,* **73**(5): 600-603.

Hutto C and Bratton T (1999). Palatability and cost comparison of five liquid corticosteroid formulations. *J. Pediatr. Oncol. Nurs.,* **6**(2): 74-77.

Ishizaka T, Miyanaga Y, Mukai J, Asaka K, Nakai Y, Tsuji E and Uchida T (2004). Bitterness Evaluation of Medicines for Pediatric Use by a Taste Sensor. *Chem. Pharm. Bull.,* **52**(8): 943-948.

Katsuragi Y, Mitsui Y, Umeda T, Otsuji K, Yamasawa S and Kurihara K (1997). Basic studies for the practical

use of bitterness inhibitors: selective inhibition of bitterness by phospholipids. *Pharm. Res.,* **14**(6): 720-724.

Katsuragi Y, Sugiura Y, Lee C, Otsuji K and Kurihara K (1995). Selective inhibition of bitter taste of various drugs by lipoprotein. *Pharm. Res.,* **12**(5): 658-62.

Keast R, Bournazel M and Breslin P (2003). A psychophysical investigation of binary bitter-compound Interactions. *Chem. Senses,* **28**: 301–313.

Lugaz O, Pillias A-M, Boireau-Ducept N and Faurion A (2005). Time–intensity evaluation of acid taste in subjects with saliva high flow and low flow rates for acids of various chemical properties. *Chem. Senses,* **30**: 89–103.

Meadows M (2003). Drug Research and Children. *U.S. Food and Drug Administration FDA Consumer Magazine* January-February 2003.

Mitchell JC and Counselman FL (2003). A taste comparison of three different liquid steroid preparations: prednisone, prednisolone, and dexamethasone. *Acad. Emerg. Med.,* **10**: 400-403.

Mojet J, Heidema J and Christ-Hazelhof E (2003). Taste perception with age: generic or specific losses in supra-threshold intensities of five taste qualities? *Chem. Senses,* **28**: 397–413.

Nahata M (1999). Lack of pediatric drug formulations. *Pediatrics,* **104**: 607-609.

Nakamura T, Akiyoshi T, Tanaka N, Shinozuka K, Matzno S, Nakabayashi T, Matsuyama K, Kashiwayanagi M and Uchida T (2003). Effect of quinine solutions on intracellular Ca^{2+} levels in neuro-2a cells-conventional physiological method for the evaluation of bitterness. *Biol. Pharm. Bull.* **26**(11): 1637-1640.

Nanda A (2000). Development and evaluation of novel taste masked formulations of dicyclomine hydrochloride. *M. S. (Pharm.) Thesis,* NIPER, S. A. S. Nagar, Punjab, India.

Nunn T and Williams J (2005). Formulation of medicines for children. *Br. J. Clin. Pharmacol.,* **59**(6): 674-676.

Ogawa T, Nakamura T, Tsuji E, Miyanaga Y, Nakagawa H, Hirabayashi H and Uchida T (2004). The combination effect of L-arginine and NaCl on bitterness suppression of amino acid solutions. *Chem. Pharm. Bull.,* **52**(2): 172-177.

Saito M, Hoshi M, Igarshi A, Ogata H and Edo K (1999). The marked inhibition of the bitter taste of polymyxin B sulfate and trimethoprim x sulfamethoxazole by flavored BMI-60 in pediatric patients. *Biol. Pharm. Bull.* **22**(9): 997-998.

Salazar de Saavedra M and Saavedra C, II (2000). Application of a sensorial response model to the design of an oral liquid pharmaceutical dosage form. *Drug Dev. Ind. Pharm.,* **26**(1): 55-60.

Samulak K, El-Chaar G and Rubin L (1996). Randomized, double blind comparison of brand and generic antibiotic suspensions:A study of taste in adults. *Pediatr. Infect. Dis. J.,* **15**: 14-17.

Schiffman S, Zervakis J, Suggs M, Budd K and Iuga L (2000). Effect of tricyclic antidepressants on taste responses in humans and gerbils. *Pharmacol. Biochem. Behav.,* **65**(4): 599-609.

Schwartz R (2000). Enhancing children's satisfaction with antibiotic therapy: A taste study of several antibiotic suspensions. *Curr. Therap. Res.,* **61**(8): 570-581.

Shohan E, Junhins E, Corneli H and Schunh J (2001). Taste test: Children rate flavouring agents used with activated charcoal. *Arch. Pediat. Adolesc. Med.,* **155**: 683-686.

Sjvall J, Fogh A, Huitfeldt B, Karlsson G and Nylen O (1984). Methods for evaluating the taste of paediatric formulations in children: a comparison between the facial hedonic method and the patients own spontaneous verbal judgement. *Eur. J. Ped.,* **141**: 243-247.

Steele R, Thomas M and Begue R (2001). Compliance issues related to the selection of antibiotic suspensions for children. *Pediatr. Infect. Dis. J.,* **20**: 1-5.

Tanigake A, Miyanaga Y, Nakamura T, Tsuji E, Matsuyama K, Kunitomo M and Uchida T (2003). The bitterness intensity of clarithromycin evaluated by a taste sensor. *Chem. Pharm. Bull.,* **51**(11): 1241-1245.

Thyssen A, Remmerie B, D'Hoore P, Kushner S and Mannaert E (2007). Rapidly disintegrating risperidone in subjects with schizophrenia or schizoaffective disorder: A summary of ten phase I clinical trials assessing taste, tablet disintegration time, bioequivalence, and tolerability. *Clin. Therapeutics,* **29**(2): 290-304.

Toscani M, Drehobl M, Freed J and Stool S (2000). A Multicenter, randomized, comparative assessment in healthy pediatric volunteers of the palatability of oral antibiotics effective in the therapy of otitis media. *Curr. Therap. Res.,* **61**(5): 277-285.

Tsuji E, Uchida T, Fukai A, Fujii R and Sunada H (2006). Evaluation of bitterness suppression of macrolide dry syrups by jellies. *Chem. Pharm. Bull.,* **54**(3): 310-314.

Uchida T, Kobayashi Y, Miyanaga Y, Toukubo R, Ikezaki H, Taniguchi A, Nishikata M and Matsuyama K (2001). A new method for evaluating the bitterness of medicines by semi-continuous measurement of adsorption using a taste sensor. *Chem. Pharm. Bull.,* **49**(10): 1336-339.

WHO (1998). Quality control methods for medicinal plant material. WHO Geneva, pp 38-40.

Worlington J (2001). A matter of taste. Pharmaeutical Executive April 2001 http://www.pharmexec.com/pharmexec/article/articleDetail.jsp?id=2477 Accessed on March 18, 2007.