Research & Reviews: Journal of Pharmacy and Pharmaceutical Sciences ISSN: 2320-1215

Taste Masking of Oral Pharmaceutics: A Review

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Review Article

Received: 02-Mar-2022, Manuscript No. JPPS-23-93736; **Editor assigned:** 08-Mar-2022, Pre QC No. JPPS-23-93736 (PQ); **Reviewed:** 22- Mar-2022, QC No. JPPS-23-93736; **Revised:** 29-Mar-2023, Manuscript No. JPPS-23-93736 (R); **Published:** 26-Apr-2022, DOI: 10.4172/2320-1215.12.2.001

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Citation: Roy S, et al. Taste Masking of Oral Pharmaceutics: A Review. 2023;12:001.

ABSTRACT

Taste, texture and smell are the crucial factors in development of oral dosage forms. Taste is a factor which influences product quality and hence affects the therapeutic value, compliance, and acceptance of the patient, and so taste masking of obnoxious drugs is important as most of them are administered orally. This reason is an initiative for the development of various taste masking technologies through which the characteristics of the dosage form is improved. The main objective of this review is to explore taste masking and its various methodologies for increasing palatability for oral pharmaceuticals along with evaluation.

Keywords: Taste masking; Taste Masking Techniques; Bitter drugs; Patient compliance; Taste assessment

INTRODUCTION

Taste, texture and smell are the crucial factors in development of oral dosage forms. Taste is a factor which influences product quality and hence affects the therapeutic value, compliance, and acceptance of the patient, and so taste masking of obnoxious drugs is important as most of them are administered orally. This reason is an initiative for the development of various taste masking technologies through which the characteristics of the dosage form is improved. The main objective of this review is to explore taste masking and its various

methodologies for increasing palatability for oral pharmaceuticals along with evaluation [1].

Factors that are taken in consideration during the process of taste masking are:

- Extent of the bitter taste
- Required dose load and dosage form
- Drug particulate shape and size distribution
- Drug solubility and ionic characteristics
- Required disintegration and dissolution rate of the finished product
- Desired bioavailability and release profile

Properties of an ideal taste masking process:

- No adverse effect on drug bioavailability
- Involve the least number of equipment and processing steps
- Easy to prepare and least manufacturing cost
- Can be carried out at room temperature
- Require minimum number of excipients that are safe, easily available and have lower cost

Taste masking technologies

The methods commonly utilized for achieving effective taste masking include different physical and chemical methods that prevent the drug substance from interaction with the taste buds. So that different methods are available to mask undesirable taste of the drugs. A few of these are as given below [2].

LITERATURE REVIEW

The methods

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Use of flavor enhancers

Flavoring and perfuming agents can be obtained from either natural or synthetic sources. Natural products include fruit juices, aromatic oils such as peppermint and lemon oil, herbs, spices and their distilled fractions. They are available as concentrated extracts, alcohol or aqueous solutions, syrups or spirits. The use of flavor enhancers are limited to substances with an unpleasant taste and is not applicable to the oral administration of very bitter-tasting medicines such as various antibiotics. It is important to understand that only the soluble part of the drug can produce a taste sensation [4]. The addition of flavors and sweeteners is the simplest and easiest approach to taste masking, especially in the case of pediatric formulations (Table 1).

Table 1. Flavoring agents for taste masking.

Basic taste	Masking agents
Sweet	Vanilla, bubble gum, grapefruit
Acid	Lemon, lime, orange, cherry, grapefruit
Metallic	Grape, marsh, mellow, gurana, berries, mints
Bitter	Liquorices, coffee, chocolate, mint, grapefruit cherry, peach, raspberry, orange, lemon, lime

Polymer coating of drugs

Coating is an extremely useful method for number of applications within the pharmaceutical field. By planning the correct type of coating material it is possible to completely mask the taste of a bitter drug. Any nontoxic polymer that is insoluble at basic pH and soluble at acidic pH, would be an acceptable alternative for taste masking [5].

Taste masking of ibuprofen has been effectively accomplished by utilizing the air suspension coating technique to form microcapsules, which comprises a pharmaceutical core of a crystalline ibuprofen and methacrylic acid copolymer coating that provides chewable taste veiled characteristics. Various inert coating agents like starch; povidone, gelatin, methylcellulose, ethyl cellulose etc. are utilized for coating drug particles. One of the most effective method of drug particle coating is the fluidized bed processor [6].

Inclusion complexes

In the formation of the inclusion complex, the drug molecule fits into the cavity of the complexing agent i.e., the host molecules forms a stable complex. Chelating agent can mask the bitterness of a drug by either decreasing its oral solubility when ingested or by decreasing the amount of drug particles exposed to the taste buds, thereby reducing the perception of bitterness. Betacyclodextrin is the most widely used complexing agent for inclusion complexes. The strong bitter taste of carbapentane citrate syrup was reduced to about 50% by forming a 1:1 complex with cyclodextrin [7].

Microencapsulation

Microencapsulation process has been characterized as a means of applying relatively thin coating to small particles of solid, droplets of fluid and dispersion. This prepare can be utilized for masking of bitter tasting drugs microencapsulating drug particles with different coating agents. Coating agents employed includes gelatin, povidone, hydroxy propyl methylcellulose, ethyl cellulose, bees wax, carnauba wax, acrylics and shellac. Bitter tasting drugs can first be encapsulated to produce free flowing microcapsules, which can then be blended with other excipients and compressed into tablets. Microencapsulation can be accomplished by variety of methods including air suspension, coacervation, phase separation, spray drying and coagulating, pan coating, solvent evaporation and multiorifice centrifugation techniques [8].

Solid dispersion

They are dispersions of one or more active ingredient in an inert carrier or matrix in solid state, and insoluble matrices may be used to mask the taste of bitter drugs. Carriers used in solid dispersion systems include povidone, polyethylene glycols, hydroxypropyl methylcellulose, urea, mannitol and ethylcellulose [9].

Multiple emulsions

A novel technique for taste masking agents using multiple emulsions was prepared by dissolving the drug in the inner aqueous phase of w/o/w emulsion under conditions of good storage stability. The formulation is designed to release the drug through the oil phase in the presence of gastrointestinal fluid [10].

Development of liposome

Another way of masking the unpleasant taste of therapeutic agent is to entrap them into liposome. For example, incorporation into a liposome product prepared with egg phosphatidyl choline masked the bitterness of chloroquine phosphate in a pH 7.2 HEPES (N-2-hydroxyetylpiperzine-N'-2-ethane sulfonic acid) buffer [11].

Prodrug

Prodrugs are chemically modified, inert prodrugs, that release pharmacologically active parent drug during biotransformation. Examples of drug with improved taste are given below (Table 2).

Table 2. Prodrugs with improved taste.

Parent drug	Prodrug with improved taste
Chloramphenicol	Palmitate ester
Clindamycin	Palmitate ester
Triamcinolone	Diacetate ester

Anthelmintic activity

This technique using the solvent mixture of water soluble polyethylene glycol to soften the active blend, using methanol to expel the softened mass from the extruder or syringe to get even segments of the cylinder of the product using heated blade to form tablets. The dry cylinder can also be used to coat the granules of the bitter tasting drugs, thereby masking their bitterness [12].

Ion exchange resin complexes

Ion exchange resins are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium. The resulting ion exchange is reversible and stiochiometric with the displacement of one ionic species by another [13]. Synthetic ion exchange resin has been used in pharmacy and medicine for taste masking or controlled release of drug as early as. Some bitter drugs whose taste has been masked by using ion exchange resin are listed in the (Table 3).

Table 3. Bitter masked by ion exchange resin.

Drug	Ion exchange resin
Norfloxacin	Indion 204 (weak cation exchange resin)
Roxithromycin	Indion 204 (weak cation exchange resin)
Ciprofloxacin	Indion 234 (weak cation exchange resin)
Chloroquine phosphate	Indion 234 (weak cation exchange resin)
Buflomedil	Amberlite IRP-69
Chlorepheniramine maleate	Indion CRP-244, Indion CRP-254
Diphenhydramine HCL	Indion CRP-244, Indion CRP-254
Ranitidine	Indion-234, cation anion exchange resin

Ion Exchange Resins (IER) have received considerable attention from pharmaceutical scientists because of their versatile properties as drug delivery vehicles.

Several ion exchange resin products for oral and parenteral administration have been developed for immediate release and sustained release purposes. Recent research IER has been found to be equally suitable for drug delivery technology includes sustained release, transdermal, nasal, topical and taste masking [14].

DISCUSSION

In vivo evaluation

Panel testing (human subject): With prior consent, on a trained taste panel of 5-10 healthy volunteers with sensual sensations. When the dosage form was placed in the mouth for 60 seconds, the bitterness recorded against pure drug using a numerical scale [15].

The numerical scale may bears values as 0=pleasant, 1=tasteless, 2=no bitter but after taste give bitterness, 3=immediately gives bitterness, 4=slightly bitter, 5=extremely bitter. Then taste the test solution and evaluate it on the same scale to assess its bitterness. Reference reports a panel test of all taste mask drugs being evaluated.

Measurement of frog taste nerve responses: In this method, an adult bullfrog is anesthetized intraperitoneally and the glossopharyngeal nerve is anesthetized. Then find the surrounding tissue, dissect it, and cut it proximally. AC amplifiers and electronic integrators are used to amplify and integrate neural impulses, respectively. The peak height of the integrated response is then considered the magnitude of the response [16].

In vitro evaluation

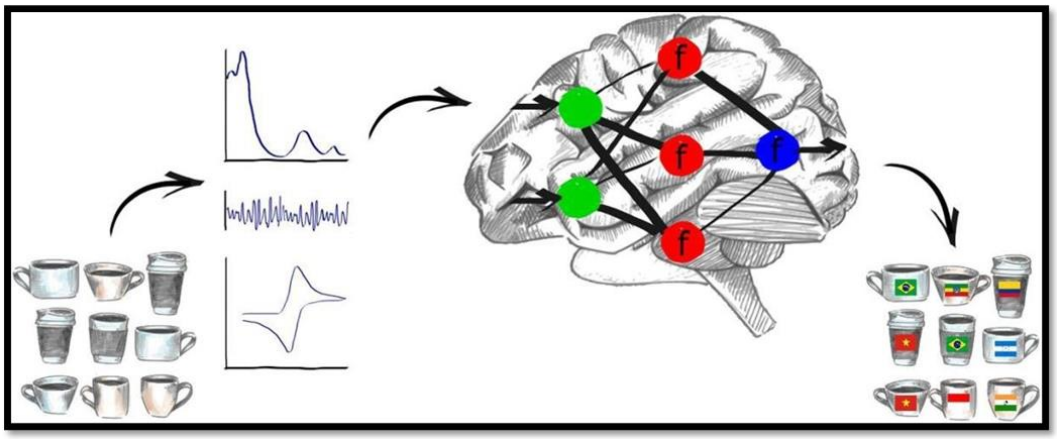
Electronic/artificial tongue: The electronic tongue is an analytical instrument encompassing an array of nonspecific, low- selective, chemical sensors with high stability and cross sensitivity to different species in solution and an appropriate method of PARC and/or multivariate calibration for data processing [17].

The working principle of an electronic tongue system (Figure 1) was inspired by biological recognition where information is gathered with the use of arrays of non-specific sensors in the tongue and the data is subsequently processed in the brain. The Physical, chemical and biochemical properties of the samples are measured by means of an array of sensors, which translate those specific attributes to an analytical signal (optical,

electrophysiological, electrochemical etc.).

The obtained data is then analysed by means of chemometric methods and artificial intelligence to achieve a similar goal, *i.e.,* discriminate, identify or quantify the sample, which provide final information about the sample for example discriminate tea samples by their geographical origin (Figure 1).

Figure 1. Working principle of electronic tongue.



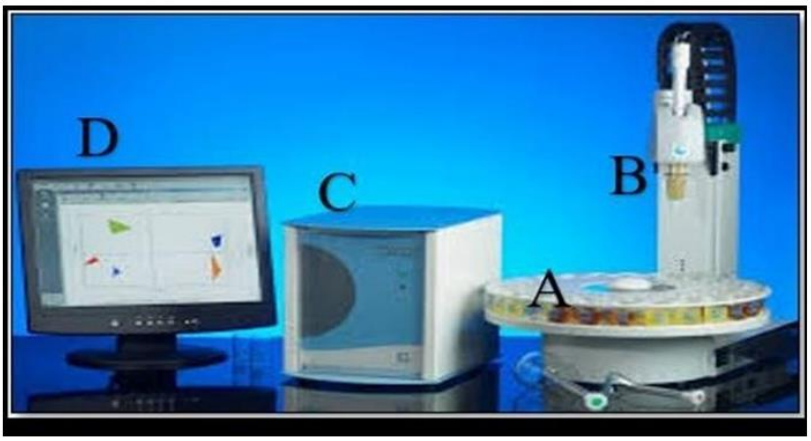
Sensor arrays of this kind initially appeared in the 1990's and were largely applied for the analysis of ions and heavy metals as well as evaluation of taste and spoilage of food products. Mimicking human taste is advantageous in circumstances when human expert panels should not or cannot be applied, because of process conditions as in instance of automatic process control especially on an industrial scale; poisonous/extreme condition samples e.g., repetitive tasting of drugs and pharmaceuticals; economic bases, defined in terms of time or financial expenses.

Sensors employed in the electronic tongue systems range from electrochemical (potentiometric, amperometric, voltammetric, impedimetric, conductometric) through gravimetric to optical (absorbance, luminescence, reflectance etc.). An ideal matrix should be composed of both selective and cross sensitive sensors. According to IUPAC report, cross-sensitivity is an ability of a sensor to respond reproducibly to a number of different analytes in the solution. Generally, electronic tongue systems are built from few to dozens of sensors of a single type, the most common being potentiometric and voltammetric. The first electronic tongue that became commercially available in the market was constructed by Toko and co-workers. Taste Sensing Systems (intelligent sensor technology inc., Atsugi-shi, Kanagawa, Japan) are established on Toko's idea and consist of 7 potentiometric electrodes with lipid polymeric membranes (Figure 2).

Figure 2. TS-5000Z taste sensing system, intelligent sensor technology inc., Japan.

Another eminent distributed commercial tongue is astree II (alpha MOS, toulouse, France). It is composed of 7 Ion Selective Field Effect Transistors (ISFET) and is devoted to discriminate samples according to their taste properties (Figure 3).

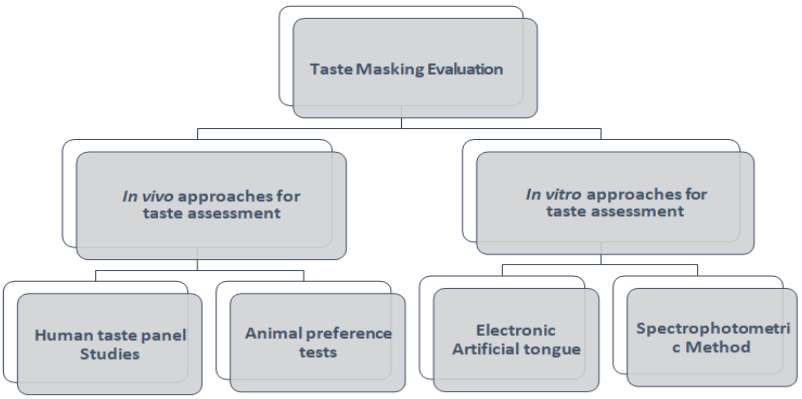
Figure 3. Alpha MOS astree II parts: A) liquid autosampler with a capacity for 16 bakers, B) electrochemical sensor array, C) acquisition unit, D) astree software V12.4 (alpha MOS).



Spectrophotometric method

A established quantity of the taste masked formulation is mixed with 10 ml of distilled water in a 10 ml syringe by revolving the syringe, end to end; five times in 30 seconds. The filter medium is then used to filter the test medium, accompined by spectrophotometric determination of the concentration of the drug in the filtrate. If this concentration is below the threshold concentration, it may be concluded that the bitter taste would be masked *in vivo*. This technique has been applied to assess the taste masked granules of sparfloxacin, with threshold concentration being 100 µg/ml (Figure 4).

Figure 4. Explain the various methods of taste masking of evulations.



CONCLUSION

In this article we have made an attempt to explain the various methods, that may be suitable for taste masking of bitter drugs. There are many techniques to effectively mask the unpleasant taste of a drugs as explained, but it requires proficient application that does not affect the bioavailability of the drug. By applying these techniques and properly assessing the effect of masking the taste, product preferences can be significantly improved. In addition, the development of taste masking methods requires good technical skills and the need for extensive experimentation. The methods described in this review can be used at both laboratory scale and pilot scales.

Sensor platform are undergoing true revolution in the search of a more available, less expensive and often disposable alternatives to sophisticated equipment sensors. As a result of which recently paper was rediscovered as a valuable substrate for electronic applications, sensors and microfluidic platforms. The growing interest in paper during the last few years can be attributed to its unique structural and mechanical properties *i.e* lightness, flexibility, capillary action, high surface to volume ratio; natural origin (biodegradability), easiness of modification and availability all over the world.

The fact that electronic tongue system have great diversity of applications creates a significant demand for their future development especially in the trend of low cost diagnostic thus the electrochemical electronic tongue with integrated reference electrodes based on paper was developed. The final system included four working silver electrodes with paper based Ag/AgCl reference all integrated in one miniaturised device and was successfully applied for the analysis of beer and wine samples. Paper based colorimetric tests were also joined to form an array able to identify eleven common organic solvents. The development of paper as a tool for evaluation of taste masking still hasn't been explored to it's full potential and thus has promising future in further research.

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