

# Pop the Pills without Bitterness

## Taste-Masking Technologies for Bitter Drugs

*K Gowthamarajan, Giriraj T Kulkarni and M Narendra Kumar*

Masking the bitter taste of drugs is a potential tool for the improvement of patient compliance, which in turn decides the commercial success of the product. To improve the palatability of a pharmaceutical product, many techniques have been developed, which have not only improved the taste of the product, but also the stability of the drug in the formulation and performance of the product. This article is an attempt to review strategies, technologies and tools that are used by pharmaceutical scientists for taste-masking.

### Introduction

Taste is an important parameter in administering drugs orally. Undesirable taste is one of the important formulation problems that are encountered with many drugs. Administration of bitter drugs orally with acceptable level of palatability is a key issue for health care providers. Proven methods for bitterness reduction and inhibition have resulted in improved palatability of oral pharmaceuticals.

### Physiology of Taste

Physiologically, taste is a sensory response resulting from a chemical stimulation of taste buds on the tongue (*Figure 1*). The sense of taste is conducted to the brain by a process called taste transduction. This process begins with the interaction of tastant (i.e., food or medicine) with taste receptor cells in the taste buds. The tastant binds with G-protein coupled receptors in the cells, triggering the release of a G-protein called gustducin. Taste sensation begins when gustducin activates the effector enzymes phosphodiesterase 1A or phospholipase C  $\beta$ -2. The effector enzymes then change the intracellular levels of second messen-

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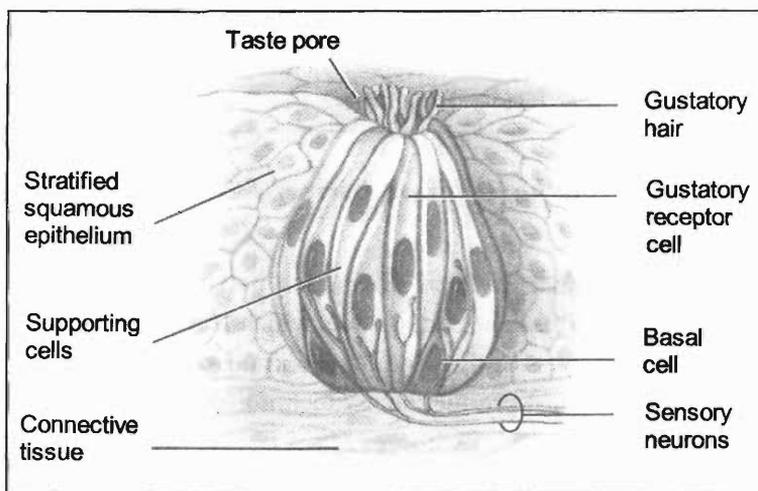
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**Figure 1. Structure of a taste bud.**



#### Keywords

Taste-masking, fluid bed coating, microencapsulation, complexation, solid dispersion.

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gers such as cyclic adenosine monophosphate (cAMP), inositol 1,4,5-triphosphate (IP<sub>3</sub>), and diacylglycerol (DAG). The second messengers activate ion channels, including calcium channels inside the cell, and sodium, potassium and calcium channels on the extracellular membrane. This ionization depolarizes the cell, causing the release of neurotransmitters that send a nerve impulse to the brain that carries the signal of taste .

Taste constitutes four primary effects, viz., sweet, sour, bitter and salty. Correspondingly, there are four different kinds of taste buds. These sensations are elicited by the tongue and interpreted by the brain. Certain areas of the tongue respond more readily to specific tastes than others. Sweet sensations are most easily detected at the tip, whereas bitterness at the back of the tongue, but salty sensations are usually detected at the tip and the sides of the tongue. During ingestion, taste buds react to soluble substances. The resulting sensations are transmitted to the brain by the ninth cranial nerve and tastes are detected. The sensitivity of the tongue to different sensations varies widely among individuals.

#### Chemistry of Taste

**Sour:** Sour stimuli in foods, such as in vinegar (acetic acid), lemon (citric acid), and apple (malic acid) are easily identifiable.

All sour substances contain acids that generally ionize in aqueous solution to produce hydrogen ions. Therefore the higher the concentration of hydrogen ions, the stronger is the sourness. Sour taste is not only dependent on hydrogen ions, but also on lipid solubility. A higher lipid solubility of the acids provides for greater concentrations at taste receptors, accounting for the increase in sour sensation.

**Salty:** It has been shown that cationic species are partially responsible for the salt solutions. Sodium chloride has a typical salty taste. Chlorides of potassium, ammonium and calcium have a similar salty taste, but their solutions taste differently. Most halide salts (sodium chloride, sodium bromide, potassium chloride and sodium iodide) have a dominating salty taste. Potassium bromide and ammonium iodide have a salty, bitter taste but potassium iodide is intensely bitter, which indicates that the taste sensations of salts shift to bitterness as molecular weight increases.

**Sweet:** Sweet is produced by a wide variety of compounds, many of which do not have any apparent structural similarity. The two most common sweet substances, sugars and glycerin, are polyhydric alcohols, containing  $-\text{CH}_2\text{OH}$  groups, which contribute significantly to sweetness. Saccharin, which has no  $-\text{OH}$  group, is intensely sweet, but has a bitter after-taste. In contrast, naturally occurring glycosides are bitter. Some amino acids, for example, glycine, are sweet. The sodium and calcium salts of cyclohexyl sulfamic acid (cyclamates) and the dipeptide ester aspartame are roughly thirty times sweeter than sugar and have been used as sugar substitutes.

**Bitter:** A bitter taste, like sweet taste, is commonly found in a wide variety of compounds, most of which are salts of organic and inorganic compounds. Bitterness is often associated with the nitro group, and the presence of two or more nitro groups in a molecule results in a bitter taste. Structurally unrelated compounds, such as esters of aromatic acids, lactones, and sulfur-containing aliphatic compounds, exhibit bitterness.

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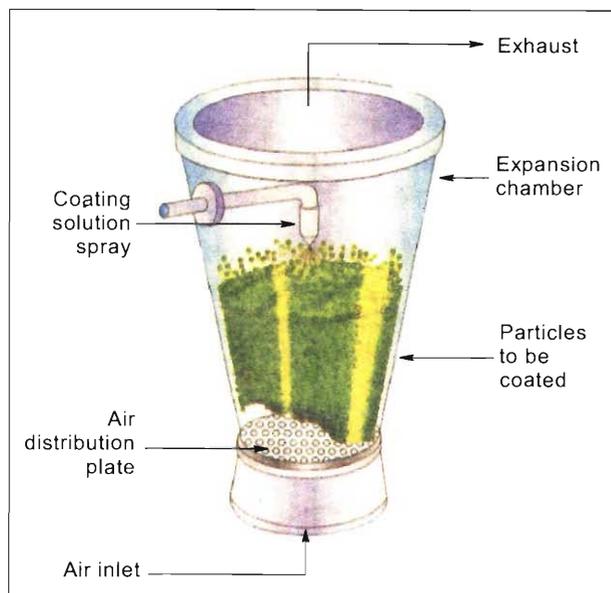
### Taste-masking Techniques

Various methods are available to physically mask the undesirable taste of drugs, some of which are described below.

#### Coating of Drug Particles

Various inert coating agents can be used to coat bitter drugs. They include starches, polyvinyl pyrrolidones (povidone) of various molecular weights, gelatin, methylcellulose, hydroxy methylcellulose, microcrystalline cellulose and ethyl cellulose. These coating agents simply provide a physical barrier over the drug particles. One of the most efficient methods of drug particle coating is the fluidized bed coating. In this approach, powders as fine as 50  $\mu\text{m}$  are fluidized in an expansion chamber by means of heated, high-velocity air, and the drug particles are coated with a coating solution introduced usually from the top as a spray through a nozzle (*Figure 2*). Increasing the length of the coating cycle can increase coating thickness. Taste-masking of Ibuprofen has been successfully achieved by this technique to form microcapsules.

**Figure 2. Schematic representation of fluidized bed coating technique.**



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#### Microencapsulation

Microencapsulation is a process of applying relatively thin coating to small particles of solids, droplets of liquids and dispersions, using various coating agents, such as gelatin, povidone, hydroxyethyl cellulose, ethyl cellulose, bees wax, carnuba wax and shellac.

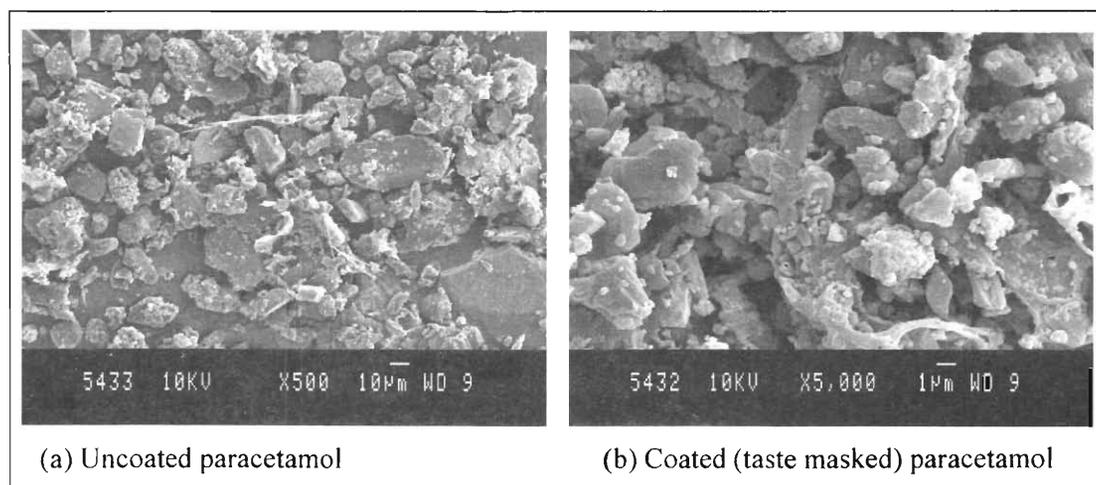
Bitter-tasting drugs can be first encapsulated to produce free flowing microcapsules, which are then blended with other excipients and compressed into tablets. Microencapsulation also increases the stability of the drug. It can be accomplished by a variety of methods, including air suspension, coacervation-phase separation, spray drying and congealing, pan coating, solvent evaporation and multi-orifice centrifugation techniques. Among these, coacervation-phase separation technique appears to be more relevant and suitable for taste-masking applications. It has been reported that the bitter taste of paracetamol was completely masked on microencapsulation using cellulose-wax combination. In a study carried out in our laboratory, microencapsulation of paracetamol using chitosan completely masked the bitter taste of paracetamol. The scanning electron micrographs of pure paracetamol and taste-masked paracetamol powders are shown in *Figure 3*.

### *Inclusion Complexes*

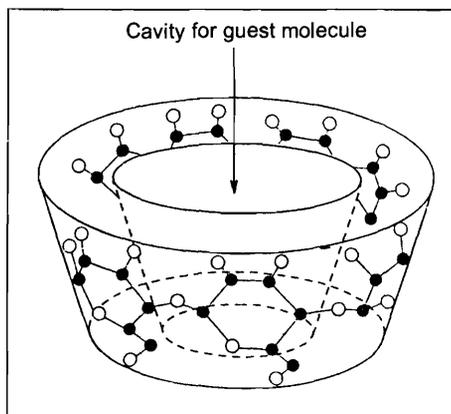
In this process, the drug molecule fits into the cavity of a complexing agent forming a stable complex. The complexing agent is capable of masking the bitter taste of a drug by either decreasing its oral solubility on ingestion, or decreasing the amount of drug particles exposed to taste buds, thereby reducing the perception of bitter taste.  $\beta$ -Cyclodextrin is the most widely

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*Figure 3. Scanning electron micrograph of uncoated (bitter) and coated (taste-masked) paracetamol particles.*



**Figure 4. Structure of  $\beta$ -cyclodextrin.**



used complexing agent for inclusion type complexes. It is a sweet, nontoxic, cyclic oligosaccharide derived from starch. Cyclodextrin forms inclusion complexes with organic molecules both in solid state and in solution. The inclusion complexes with cyclodextrin owe their existence to van der Waals forces between the host and guest (*Figure 4*).

### ***Molecular Complexes of Drugs with Other Chemicals***

The solubility and absorption of drugs can be modified by the formation of molecular complexes. Lowering drug solubility through molecular complexation can decrease the intensity of bitterness. The bitterness of caffeine was completely masked by the formation of a molecular complex of caffeine and gentisic acid in 1:1 and 1:2 molar ratios. The complex was prepared by rapid cooling of the hot aqueous solution of the mixture. The resulting microcrystalline powder precipitate was washed with water and dried under vacuum.

### ***Solid Dispersions***

They are dispersions of one or more active ingredient in an inert carrier or matrix in solid state, and insoluble or bland matrices may be used to mask the taste of bitter drugs. Carriers used in solid dispersion systems include povidone, polyethylene glycols of various molecular weights, hydroxypropyl methylcellulose, urea, mannitol and ethylcellulose. Various approaches for preparation of solid dispersion are described below.

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**Melting method:** In this method, the drug or drug mixture and a carrier are melted together by heating. The melted mixture is cooled and solidified rapidly in an ice bath with vigorous stirring. The final solid mass is crushed and pulverized.

**Solvent method:** In this method, the active drug and carrier are dissolved in a common solvent, followed by solvent evaporation and recovery of the solid dispersion.

**Melting-solvent method:** In this method the drug in solution is incorporated into a molten mass of polyethylene glycol at a temperature below 70°C without removing the solvent.

### ***Drug-Resin Complexes***

When an ionizable drug reacts with a suitable ion exchange resin, the drug-resin complex formed is known as a 'drug resinate'. Since the drug resinate is insoluble, it has virtually no taste, so that even very bitter drugs lose their taste when converted into a drug resinate with the correct selection of the ion exchange resin. The drug resinate can be made sufficiently stable that it does not break down in the mouth so that the patient does not taste the drug when it is swallowed. However, when the drug resinates come in contact with gastrointestinal fluids, usually the acid of the stomach, the complex is broken down quickly and completely. The drug is released from resinate directly into the solution and then absorbed in the usual way. The resin passes through the gastrointestinal tract without being absorbed.

### ***Formation of Salts or Derivatives***

In this approach, an attempt is made to modify the chemical composition of the drug substance itself, so as to render it less soluble in saliva and thus make it less sensitive to the taste buds. Aspirin tablets can be rendered tasteless by making magnesium salt of aspirin. D-chlorpheniramine maleate is a taste-masked salt of chlorpheniramine. The alkyloxy alkyl carbonates of clarithromycin have remarkably alleviated bitterness and

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**Suggested Reading**

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***Use of Amino Acids and Protein Hydrolysates***

By combining amino acids or their salts with bitter drugs, it is possible to substantially reduce the bitterness. Some of the preferred amino acids include sarcosine, alanine, taurine, glutamic acid, and glycine. The taste of ampicillin improved markedly by preparing its granules with glycine and mixing them with additional quantity of glycine, sweeteners, flavors and finally compressing them into tablets.

***Taste-masking by Viscosity Modifications***

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 carboxy methylcellulose. Surprisingly, it has been observed that the high viscosity liquid excipient base provides taste-masking benefits to such an extent that extra strength compositions can be prepared with high concentrations of bitter tasting ingredients. For example, guaifenesin, which is normally administered in doses of not more than 100 mg in 5 ml of liquid, may be administered in doses of 200 mg/5 ml, without the feel of bitter taste.

**Conclusion**

For better taste-masking, effective techniques are being developed constantly in the pharmaceutical industry. Presently the use of these techniques depends on the nature of drug. The pharmaceutical industry is in search of a universal method, which can be applied to all the drugs, a goal which is yet to be reached.

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