Taste Masking Techniques of Unpleasant Drugs

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Abstract

Background: Taste masking is one of the many processes that are used in the pharmaceutical industry. This is done with the intention masking or decreasing of a disagreeable taste or odor from the organic compounds which are usually used in the oral cavity and can be formulated by several types of techniques.

Objective: To highlight the definition and importance of taste masking, the factors that affect taste masking, the many types of taste masking techniques that can be used, and the evaluation of taste masking in vitro and in vivo evaluations.

Results: The masking of unpleasant taste or odor is important in the marketed product to improve patients' compliance, especially for pediatric and geriatric patients, because it is necessary for the improvement of the therapeutic efficacy, and that's can be obtained by several methods of taste-masking techniques; furthermore, these techniques may be simple, namely, like adding a sweetener or flavored agents, or by using other complicated methods like polymer coating, complexation, resin ionic exchange, external or internal ionic gelation, physical or chemical adsorption, granulation, microencapsulation, solid dispersion, effervescence, viscosity modification, nanosuspension, pro-drug and so on; it sometimes needs the combination of more than two methods to overcome very bad taste, and depends on the severity of the undesirable taste.

Conclusion: The undesirable taste or odor can be masked by using different types of techniques depending on the intensity of the bad taste or odor, in addition to other factors that are related to the drug itself, and the method of the dosage form that was chosen, and other factors. Taste masking was needed to improve patients' compliance with the marketed products, and that is an important factor to ensure total completion of the drug course by patients.

Keywords: Bitter taste; Patients' compliance; Taste buds; Taste masking; Unpleasant taste.

Introduction:

Taste masking is the reduction of a disagreeable taste from the organic compounds in the oral cavity. Taste masking methods aim at improving patients' compliance to achieve therapeutic efficacy. To select the most suitable technique, the following points should be considered (1,2).

The degree of bitterness: The degree of the bitter taste of the active ingredient may vary from mild to medium or extremely bitter taste. It is important to choose suitable techniques for masking the taste, i.e. a mild bitter taste can be masked by simply adding sweetening or flavoring agents while the extremely bitter taste needs other techniques like coating, ionic gelation, resin complexation, or a combination of methods to mask the taste.

The solubility of the drug: Solubility has a direct relationship with the taste bud sensation. The more soluble the drug, the higher the sensitivity of the taste buds and so more bitterness,

Dose of the active ingredient: The dose size of a drug affects the final weight of dosage form especially those that need low dose

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weight; for example, oral disintegrating film and oral disintegrating tablet, since, it is important to choose a technique that does not enlarge the required equivalent dose.

Desired release of the dosage form: Taste-masking technique should decrease the release of the drug in the oral cavity and at the same time must not affect its release in the stomach.

Dosage form requirement: Oral dosage forms like chewable, oral dispersible tablets, oral dispersible films, and suspension need masking to improve patients' compliance.

Importance of taste masking: Pediatric, geriatric, and other patients who are suffering from trouble swallowing, need a specific oral dosage form like chewable tablets, fast dissolve oral tablet/ film, or liquid dosage form. Since some drugs have undesirable tastes, taste masking becomes an important way to improve patient

compliance (3).

Different techniques are available for taste masking like the addition of sweetener and/ or flavoring agents, coating with polymer, complexation with resin or cyclodextrin, adsorption, and chemical

with resin or cyclodextrin, adsorption, and chemical reactions like pro-drug (4), so this review aimed to

Received: June 2023 Revised: April 2025 Accepted: June 2025 Published Online: June 2025 Published: July 2025 highlight the definition and importance of taste masking, the factors that affect taste masking, the many types of taste masking techniques that can be used, and the evaluation of taste masking in vitro and in vivo evaluations.

Taste buds: Taste buds are tiny gustatory sensory organs (gustatory papillae) they are primarily located on the surface of the tongue and some others are found in epithelial cells of other parts of the oral cavity like the pallet, oropharynx, and upper esophagus. They have bulb-shaped structures and each is composed of 50 - 150 bipolar cells (sensory cells), these cells together form the sensory organ. A sensory cell has trans-membrane receptors and\or ion channels in the cell membrane for specific taste stimuli and is responsible for reporting the sense of taste to the brain (5).

There are four main kinds of taste sensations: Sweet, bitter, salty, and sour. The fifth type is called "umami" and is related to tasting some amino acids. The taste of some compounds is affected by many factors related to the compound itself, like molecular weight and functional groups in the chemical structure. Salts with low molecular weight have salty taste while those with high molecular weight become bitter. Compounds containing a nitrogen group like alkaloids have a very bitter taste, while compounds with hydroxyl group tend to have a sweet taste which increases with the increasing number of this group (6).

Taste masking technologies: The most important taste-masking technologies are built on the reduction of the drug solubility in the saliva to a level below the taste threshold value. The taste threshold is a minimum concentration below which the taste of substances is not felt by taste buds. The major methods are described below (7).

Sweeteners and flavors: Sweetener: This is the most common and simplest method for taste masking but is inefficient with aggressively bitter drugs like antibiotics. It can be used with other techniques to increase their efficiency.

Two types of sweetening agents are available: Synthetic and natural with different efficiencies. Table (1) shows commonly used sweeteners with their relative sweetener to that of sucrose (8). Examples are saccharine for masking the bitter taste of zinc acetate dihydrate as lozenges and sodium saccharin for taste masking of ibuprofen as suspension (1).

Sweetener agents	R.S*	Comments	
Lactose	0.160	Need large quantity	
Mannitol	0.6	Negative heat of solution	
Sucrose	1	Most generally used	
Aspartame	200	May not be stable in solution form	
Saccharine	450	Un-agreeable after taste	
Sucralose	600	Synergistic sweetening effect	

 Table (1): Common Sweetening Agents and their Relative Sweetener (8)

* Relative Sweeteners (R.S) to the sucrose as standard of 1 for comparison.

Flavors: These are aromatic chemical compounds with a cooling effect that reduces the bitter taste and bad odor of drugs. Like sweeteners, they are also found in two types: Synthetic (vanilla) and natural (peppermint, strawberry). A combination of flavoring agents is typically employed. Selection of the favorable flavoring agent depends on the taste of the drugs, Table (2). Flavor adjuvants like menthol and chloroform act as soothing agents because of their odor and mild numbing effect on taste receptors. Aspirin-medicated floss has sodium phenolate as a numbing agent in additionally to the chocolate flavor to cover the bad taste of the drug (9).

Table (2): Selection of the Flavor (9)
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Taste sensation of drug	Recommended flavoring agents
Sweet	Vanilla, fruit and berry
Bitter	Chocolate, coffee and wild cherry
Salt	Apple and vanilla
Sour	Raspberry and citrus flavor

Coating: Polymer coating can be a suitable taste masking. Palatability is dependent on the drug, type of polymers, and method of preparation. The coating by polymer forms a barrier that eliminates the release of the drug in the mouth. Fluid bed coating is one of the common approaches because its efficiency can be applied to particles, granules, and tablets. it provides a uniform, continuous product coating, and it can be used in aqueous and organic coating (10).

Any safe and inert polymer that is not soluble at a mouth pH and is soluble at a stomach pH is suitable for taste masking. Examples are gelatin, starch, povidone and methyl or ethyl cellulose (11). Ibrahim et al used Eudragit E100 polymer for masking the bitter taste of furosemide oral disintegrating tablets, the palatability of the prepared oro-dispersible tablets (ODTs) was further improved by the addition of mannitol (12). Madgulkar et al used 10% w/w precirol ATO5 as a coating agent for the complete covering of the bitter taste for chloroquine phosphate tablets by hot melt coating which was a good method for taste masking for solid oral dosage form with less time consuming (13).

Complexation: Inclusion complexation is a route in which the guest molecule (drug) is included in the hole of the host (cyclodextrin). so that the quantity of the drug-exposed to taste buds is reduced. β -

Cyclodextrins are commonly used in industry by reason of their capacity to form inclusion complexes with a variability of molecules. It is a sweet and non-toxic oligosaccharide obtained from starch. The greatest ratio of drugs form complexes with cyclodextrins is 1:1 molar ratio (14). Dungarwal and Patil used hydroxyl-propyl β - Cyclodextrin to form a complex with rizatripan benzoate to prepare ODT with efficient masking of its bitter taste (15). Liu *et al* used β Cyclodextrin to mask the bitter taste of donepezil as an orodispersible film which was more palatable than the film prepared from its salt (16).

Resins (Ion exchange): The resins are polymers with high molecular weight and may be cationic or anionic functional groups. If the drug is cationic, an anionic resin should be used, and vice versa. After taken, the resin exchanges the active ingredient with the counter ion in the stomach, and the active ingredient is released to be absorbed. This means that for taste masking the resin inhibits the drug release at the pH of the oral cavity and essentially will not affect the release of the drug in the stomach and intestine, which is the challenge of a resin complex (17).

In this technique, the resin is suspended in the solvent that dissolves the drug. Resinat is the term used when a drug-resin complex is formed, which avoids the connection of the active ingredient with taste buds directly, and that provides masking in the bad taste of the drug when administered. Examples of ion exchange resins are dowex-50 (strong cation) and amberlite IRc 50 (weak cation) (17). Taste- masked nizatidine was prepared by Pattaraporn *et al* using dowex-50, when it was found that nizatidine – resin complex at 1:5 ratio released only 4.3% at mouth pH within five minutes while it released 99.7 % within 60 minutes at stomach pH (18).

Adsorption: This method happens via the adhesion of a substance (gasses, fluid, or solid) termed a substrate, on the surface of a solid or a liquid, termed sorbent or adsorbent, with the product of adsorption process known as "adsorbate". There are two mechanisms: Physical and chemical adsorption (19). Physical adsorption: In this mechanism the bond that connects the substrate and sorbent is a weak Van der Waals bonding, that will not affect their chemical structure. It is known as physisorption (19).

Chemical adsorption: In this mechanism, chemical bonds are formed between substrate and sorbent, which may be ionic or covalent bonds. It is also known as chemisorption (19). Adsorption of a bittertasting drug can be used to produce a drug with low solubility in saliva. This method includes adsorption of the drug by insoluble material like veegum, bentonite, silica gel, or silicates (20). Sona and Muthulingam used veegum (magnesium aluminum silicate) as a taste masking agent (adsorbent) for diclofenac sodium to prepare an ODT at different drug: veegum ratios. The optimum taste masking was obtained by 1:1.5 (drug: veegum ratio) which prevents drug release in the mouth pH for about five minutes (21). **Granulation:** Granulation is one of the simplest, costliest, and fastest of the taste masking methods and is a common processing step in the preparation of all types of tablets. Certain polymers which are insoluble in the saliva can be used as a binding and taste masking agent. Liquids and low melting point waxes such as glycerol palmitate stearate, glyceryl distearate, and steric acid are frequently used in this method to cover the bad taste by melted or wet granulation technique although these materials may affect the release of drug in the stomach. It can be used to prepare various types of tablet dosage forms like chewable tablets and ODTs (22).

Forster and Lebo used glyceryl distearate as the binder successfully to cover the unpleasant taste of ibuprofen by melt granulation technique (23).

Microencapsulation: Microencapsulation is the technique in which a very tiny particle of solids or tiny droplet of liquid is coated by a film of polymer for taste masking, increased stability, sustained release, and other purposes. Taste masking is obtained when the solubility of the drug in the oral cavity is decreased by applying this film, which also acts as a physical layer between the soluble drug and taste buds (24). Polymers like: Povidone, gelatin, methylcellulose hydroxypropyl (HPMC), ethylcellelose and bee wax are the most widely used polymers. Microcapsules can be prepared by different methods including Air suspension, pan coating, solvent evaporation, centrifuge process, coacervation and spray drying or spray congealing (25). Han et al used Eudraget E 100 to cover the unpleasant taste of lacosamide via spray drying (26).

Solid dispersion: It is the dispersion of the drug in an inactive carrier at a solid state (solid in solid) via solvent evaporation, melting, or fusion solvent method. This approach is used for many purposes such as increasing solubility, taste masking, and others. In this technique, the polymer acts as a carrier like: Eudraget EPO, Eudraget E 100, and ethyl cellulose (27). The bitter taste of ondasteron hydrochloride is completely covered via Eudraget E100 as an inert carrier at (1:2) drug: carrier ratio using solvent evaporation technique (28).

Ionic gelation: It is a chemical reaction used to encapsulate the active ingredient by insoluble gel. This method is used for masking undesirable tastes, targeting drug delivery, and sustained release preparation. In this method, alginate salts such as sodium alginate (S. Alg) react with bivalent metal ions like calcium chloride (CaCl₂) or barium chloride (BaCl₂) due to cross-linking between the carboxylate anions of alginate glucuronate and the calcium ions as shown in Figure (1) and form beads (insoluble gel) which contain the bitter active ingredient. Taste masking is obtained by decreasing the drug release in the oral cavity (29, 30).

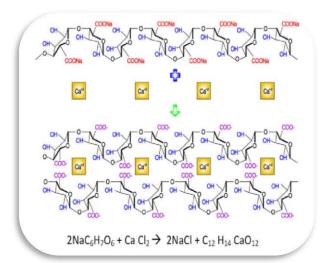


Figure (1): Crosslinking of sodium alginate with calcium chloride (31)

This technique is of low cost and is used for encapsulating active materials. It does not need a special temperature or a solvent, so it can be used for heat-sensitive materials. The main kinds are internal and external ionic gelation (32).

External gelation: External gelation is the most used method as ionic gelation to form alginate beads. Known as externally because the cross-linker (Ca⁺²) is found in solutions separated from the alginate hydrogel, expressed as liquid-liquid methods (32, 33). So, the initiation of the crosslinking of alginate hydrogel is done by diffusion of Ca⁺² ions into the spaces between the alginate polymer chains. The drug is found in the alginate hydrogel and then dropped in the gelling solution having Ca^{+2} ions. Figure (2) shows the peripheral cross-linking of the alginate drop with Ca^{+2} ions, which is the consequence in the initial formation of a semi-solid membrane covering the droplet with a liquid core. Prolonged soaking of the droplets in the hardening solution permits more diffusion of Ca⁺² through the membrane by a concentration gradient. Then, that leads to the rigidities of the droplet core. Consequently, a calcium-alginate bead is formed with the drug entangled randomly within the bead matrices (32, 33). It is still the best method of ionic gelation for its simple single-step process to formulate dissimilar particle morphologies without the requirement for a gelling initiator (32, 33).

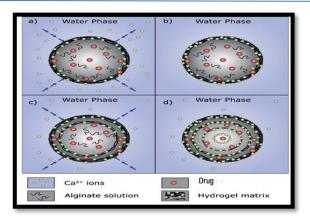


Figure (2): The mechanism of external gelation for bead formation: a alginate drop in Ca^{+2} solution, b- inner diffusion of Ca^{+2} , c- inner gelation of drop, and d- bead formation (33)

Internal gelation: It is called internal because of the generation of the cross-linker ion in the internal solution "in situ", Figure (3). Calcium and barium carbonate as insoluble salts, act as a source of cross-linking cation. Lowering the pH of the solution, leads to the release of the cation, thus solubilizing the metal salt and releasing the metallic ion (34).

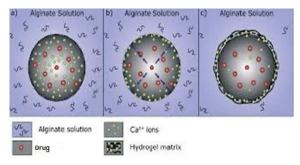


Figure (3): The mechanism of internal ionic gelation (33)

Rajmohan and Bellmer found that external gelation produced beads with an encapsulation efficiency of about 78% while the encapsulation efficiency by internal gelation was around 23% regardless of the S. Alg and CaCl₂ concentration (35). Sutriyo *et al* prepared alginate beads by external method for masking the bitter taste of melon (Momordica charantia Linn) extract at a ratio (1:2) extract: alginate at the constant concentration of (CaCl₂) solution (3%) (36).

Effervescent agents: These agents can be used in oral dosage form. They have many advantages including taste masking. They are used in a form that does not dissolve in water prior to administration. Asfor the locally acting drugs on the oral cavity or for buccal absorption like chewing gum which contains a bitter drug, sublingual tablets, and other oral administered dosage forms. They maskthe taste by generation of carbon dioxide (37). Pavani *et al* prepared metronidazole as ODT and masked its bitter taste using sodium bicarbonate: tartaric acid in a ratio (1:1.5) (38).

Viscosity modification: An increase in the viscosity with viscosity modifiers like carbohydrate or gums can decrease the diffusion of unpleasant molecules from the dosage form to the taste buds. Suspension of acetaminophen formulated with xanthan gum in a concentration of (0.1-0.2%) and microcrystalline cellulose of (0.6-1%) results in a decrease in the bad taste of the medication (39).

Other methods: There are many other approaches to mask the bitter taste none of which is specific. Some of these methods are: Nanosuspension, nanoemulsion, prodrug, and others (40). Amelian *et al* used lyophilization process for masking the bitter taste of cetirizine di-hydrochloride micro-particles to be used as ODT (41).

Evaluation of taste masking technique: There are many approaches to evaluate the taste sensation of chemical compounds and can divided into in-vivo and in-vitro methods:

In- vivo methods:

Human test panel studies

This method measures the taste sensation by asking approximately 5 or 10 healthy human volunteers, who are skilled for taste assessment with reference solutions extending their taste from tasteless to aggressive bitterness. The dosage form is placed in the mouth of volunteers for 60 seconds, then the numerical values are assigned to these tiers of bitterness e.g. scale value 0: pleasing, 1: tasteless, 2: no bitter but subsequent taste gives bitterness, 3: directly give bitterness, 4: a little bitter, 5: aggressive bitterness (28, 42).

Animal preference test

Bottle preference and conditioned taste aversion tests are used for detecting taste preference and concentration-response properties of the tastiness of compounds by animals like rats, mice, cats and dogs (43).

In-vitro methods

Multichannel taste sensor (magic tongue): Lipidpolymer membranes commonly used in pharmaceutical uses act as the taste sensor. Bitter ingredients are absorbed on the hydrophobic fragment of the membrane and change in membrane potential, produced changing in the charge density. Lipid-polymer membrane selectivity for each taste was developed by modifying both the hydrophobic interaction between the taste sensor and bitter ingredient, and the charge density of the membrane (44).

Spectrophotometric method: In-vitro taste evaluation was done by detecting the amount of drug released in phosphate buffer pH 6.8 at 37 °C for one minute to predict the amount of drug released in the human saliva. If this concentration is below the threshold concentration, it can be considered that the bitter taste is masked (43).

Conclusion:

Masking of the unpleasant taste of drugs is very important for improved patient's compliance and

therapeutic efficacy. Many techniques can be used for taste masking depending on the solubility of drugs, dosage form needed, size of the dose, and cost of the method in addition to the extent of the bitterness which are important factors in the selection of the best technique.

Authors' declaration:

We confirm that all the Figures and Tables in the manuscript belong to the current study. Besides, the Figures and images, which do not belong to the current study, have been given permission for republication attached to the manuscript

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التقنيات المستخدمة في حجب الطعم للأدوية ذات الطعم غير المرغوب به هبة محمد سوزة 1، أيمان بكر حازم²

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الخلاصة

الخلفية: حجب الطعم هي واحده من عدة طرق التي تستخدم في المصانع الدوائية التي تهدف الى حجب او تقليل الطعم او الرائحه من المركبات العضويه التي تستخدم عن طريق الفم والتي يمكن تصييغها بواسطة انواع متعددة من التقنيات.

ا**لهدف:** لتسليّط الضوّء على تعريف و اهميّة حجب الطعم, العوامل التي تَوَثّر على حجب الطعم, انواع التقنيات التي تستعمل لحجب الطعم و الأشار ه الى كيفية تقييم حجب الطعم خارج وداخل الجسم.

النتائج: أن عُملية حجب الطعم أو الرائحه غير المرغوب بها هي عملية مهمه لتسويق المنتجات الدوائيه لعلاقتها بتقبل المريض للعلاج خاصة لمرضى الاطفال و كبار السن وذلك لاهميته بتحسين الفعالية العلاجيه حيث يمكن الحصول عليها من خلال استخدام احد التقنيات المستخدمة لحجب الطعم, وهذه التقنيات ربما قد تكون بسيطه مثل اضافة المحليات او عوامل المنكهات او يمكن استخدام التقنيات الاكثر تعثيدا مثل التغليف بالبوليمر, تكوين معقدات التبادل الايوني الصمغي, عملية البلمرة الايونية الخارجية او الداخليه, الامتزاز الفيزيائي او الكيمي التشتت الصلب, الفوارات, تعديل اللزوجه المعلقات النانويه, برودرك وطرق اخرى, بعض الاحيان يتم جمع اكثر من طريقة لتغطية الطعم شديد المرارة والتي تعتمد على درجة الطعم الردئ.

الأستنتاج: الطعم او الرآنحة غير المرغوب بها في الدواء يمكن حجبها بطرق متعدده اعتمادا على درجة الطعم او الرائحه الرديئة بالاضافة الى عوامل تعود الى الدواء نفسه ونوع الشكل الصيدلاني المختار بالاضافة الى عوامل اخرى. عملية حجب الطعم مطلوبة لزيادة تقبل المريض للادوية وهذا يشكل عامل مهم للتأكد من اتمام كورس العلاج من قبل المريض.

الكلمات المفتاحيه: الطعم المر, تقبل المريض للعلاج, براعم التذوق, حجب الطعم, طعم غير مرغوب به.