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Review Article

Importance of Palatability in Oral Pharmaceutical Dosage Forms: A Comprehensive Review

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ABSTRACT

Oral palatability – the sensory perception of taste, flavor, texture and aftertaste of a medication – is a critical determinant of patient acceptability and adherence, especially for pediatric and geriatric populations. Bitter or unpleasant tastes in oral drugs often lead to refusal, incomplete dosing, or alteration of formulations, undermining therapeutic outcomes. This review synthesizes current knowledge on factors influencing palatability (drug chemistry, formulation and patient variables), illustrates taste challenges across different oral dosage forms, and details strategies to mask undesirable flavors. We describe both traditional techniques (sweeteners, coatings, microencapsulation, and complexation) and innovative methods (ion-exchange resins, prodrugs, 3D-printed multilayer designs) for taste masking, as well as evaluation approaches ranging from human sensory panels to electronic tongues and in silico models. The impact of taste on compliance is examined through clinical evidence, and emerging advances such as artificial-intelligence taste prediction and tailored 3D printing are highlighted as future solutions. Persistent challenges – including lack of standardized palatability metrics and ethical limits on testing – are discussed, underscoring the need for systematic, patient-centered approaches.

INTRODUCTION

Palatability – the overall sensory acceptability of a medication including taste, mouthfeel and aftertaste [5] – is a key factor in ensuring that patients will take their medicines as prescribed [6][7]. The human gustatory system detects five basic tastes (sweet, sour, salty, bitter, umami) via receptors on the tongue, with bitter tastes often dominating drug formulations. Ingested chemicals interact with taste receptors (e.g. bitter compounds activate TAS2R receptors and downstream ion channels) to generate taste signals [8]. As a result, many active pharmaceutical ingredients (APIs) – especially those with aromatic rings or nitrogenous heterocycles – inherently taste bitter [9]. Children

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have more taste buds and a stronger aversion to bitterness than adults [10][11]. In practice, any drug that dissolves in saliva above its human taste threshold can produce an unpleasant flavor, whereas poorly soluble or highly lipophilic APIs may evade immediate taste detection [12][1].

Poor taste perception has a profound impact on medication adherence. Studies consistently link bad taste to skipped doses and treatment failures. For example, a scoping review of pediatric medicines found that 64% of studies reported poor palatability causing children to reject medications, and 27% reported taste as a direct barrier to adherence [1]. In one survey of commonly prescribed pediatric antibiotics, 11–56% of children "resented or refused" the medication due to taste, resulting in only 67–85% completing the treatment [13][2]. Regulatory and clinical guidelines now emphasize palatability testing for pediatric drugs, recognizing that "medicines cannot work unless correctly used by the patient" [14][7]. Historically, manufacturers often neglected taste ("the worse the taste, the better the cure"), but modern practice treats palatability as a critical quality attribute that can affect therapeutic outcomes and product success [15][7]. In summary, understanding the interplay of drug chemistry, formulation design and patient factors in taste perception is essential for developing acceptable oral medications [16][10].

Factors Affecting Palatability of Oral Pharmaceutical Dosage Forms

Palatability arises from a complex interplay of factors that can be grouped into drug-related, formulation-related, dosage-form-related, and patient-related domains [17][18].

Drug Chemistry: The inherent taste of an API depends largely on its molecular structure. Certain structural motifs – for example, aromatic rings, basic amines or hydroxyl groups – often correlate with bitterness [12]. Taste intensity generally increases with the amount of drug released in saliva: rapidly dissolving drugs at concentrations above their human taste threshold elicit stronger flavors, while drugs that are poorly water soluble or remain encapsulated have reduced oral taste [12]. Chemical modifications like salt formation or prodrug derivatization can alter an API's solubility and charge, thereby modulating its taste. For instance, converting an API to an ester prodrug can mask a bitter functional group until after it is absorbed [19][20].

Formulation Excipients and Release Kinetics: Excipients and design elements control how much drug contacts the taste buds. Fast-release formulations (e.g. syrups, dispersible tablets) expose taste receptors to the full drug dose immediately, whereas viscous vehicles or controlled-release matrices slow release in the mouth, lowering the taste impact [21]. Thickeners and gel-formers increase saliva viscosity, hindering drug diffusion to the tongue [21]. Polymers (cellulose, pH-sensitive coatings) can act as barriers, holding drug in an insoluble form until swallowing [21][22]. Manipulating pH can also mask or reduce bitterness (a slightly sour pH sometimes suppresses bitterness). In short, any strategy that keeps the dissolved drug concentration below its taste threshold in saliva will improve palatability.

Dosage Form and Route: The choice of oral dosage form dictates how and where the drug is experienced. Liquids (solutions, syrups, suspensions) typically pose the greatest taste challenge since the drug is already dissolved and immediately contacts taste buds [23]. Orally disintegrating tablets (ODTs) and oral films dissolve in the mouth without water; by design they release drug in the oral cavity, requiring

especially robust taste control [15]. Chewables and medicated gums are intended to be chewed, so drug is continuously released in saliva and must be physically entrapped or flavor-masked to avoid detection [24]. Capsules and coated tablets rely on intact shells to prevent taste; however, if split, chewed or improperly dissolved, their bitter core is exposed. Conversely, traditional swallowable tablets or capsules can bypass taste entirely when taken whole, but they must dissolve further down the GI tract – necessitating effective coatings to prevent early release in the mouth. Other specialized forms include effervescent tablets (use rapid fizz and strong citrus/mint flavors to distract from taste) and mini-tablets (often individually small and sweet-coated to minimize bitterness). In summary, any oral form that dissolves or breaks in the mouth requires intentional taste-masking design, whereas swallowable forms hinge on coatings or delayed release.

Patient Factors: Individual differences play a significant role. Children are particularly sensitive to bitter tastes and often have no tolerance for unpleasant flavors [11][16]. The elderly or patients with chronic illness may have reduced gustatory sensitivity, but issues like xerostomia or dysphagia introduce concerns about mouthfeel (e.g. grittiness or viscous coatings) that also affect palatability [25][26]. Genetic variability (supertasters with extra TAS2R receptors) can make some individuals extremely sensitive to bitterness [12]. Cultural dietary exposure to bitter foods (e.g. coffee, dark chocolate, certain vegetables) can influence what tastes are considered acceptable, meaning flavor preferences vary globally. Finally, disease states (nausea, inflammation) can alter taste perception or tolerance. In combination, these factors determine whether a given formulation is perceived as pleasant, tolerable or unacceptable by different patients.

Secondary Sensations: Beyond the five basic tastes, mouthfeel and aftertaste contribute to overall palatability. Texture issues (chalkiness, pill residue, astringency) can be off-putting even if the initial taste is acceptable [26]. Cooling or warming excipients (e.g. menthol, capsaicin derivatives) can produce additional sensations that affect liking, for better or worse. Aftertaste – the lingering sensation after swallowing – is crucial: a brief initial sweetness may not override a long bitter aftertaste. Manufacturers thus also consider coating integrity (to prevent any delayed release in the mouth), use of flavor modulating agents, and minimization of residual mouth sensations.

In sum, palatability depends on the interplay of drug chemistry, formulation design (excipients, release profile, form factor), and patient-specific variables [12][18]. A bitter API might be perfectly tolerable in an intact capsule for a healthy adult, but it becomes unacceptable in a pediatric syrup unless extensively masked [16][18]. Understanding these factors informs the choice of taste-masking strategies during development.

Palatability Issues in Different Oral Dosage Forms

Each oral dosage form presents distinct challenges for taste and mouthfeel:

Liquid Formulations (Solutions, Syrups, Suspensions): These give the drug instant access to taste receptors. Any dissolved bitter or sour APIs are sensed immediately. To counteract this, formulators commonly add sweetening agents (sugars, sugar alcohols or high-potency sweeteners) and flavor extracts (fruit, vanilla, mint, etc.) to syrups [27][28]. Viscosity enhancers (gums, cellulose) are included to slow drug diffusion to the tongue. However, masking very strong bitter APIs often requires more than sweetness – for example, using bitter blockers

(like cyclodextrin inclusion complexes) or complex flavor blends. Preservatives and excipients in suspensions can themselves have sour or medicinal notes, so additional flavor balancing is frequently needed. In practice, almost every pediatric syrup requires significant taste-masking effort, and some stubborn APIs (e.g. certain liquid antibiotics) remain a "nightmare" to formulate [28][7].

Orally Disintegrating Tablets (ODTs) and Films: ODTs and ODFs dissolve or disintegrate directly in the mouth without water, maximizing patient convenience but also exposing the drug fully to taste buds. Such forms often incorporate effervescent ingredients (to produce a pleasant fizz) or foaming agents to distract the tongue [15]. Polymer matrices or ion-exchange resins can bind the API until after swallowing. Recent advances have exploited 3D printing: for instance, instant-dissolving printed tablets with highly porous structures dissolve quickly (limiting bitter contact time) and can be printed in fun shapes or colors to appeal to children [15][29]. Oral films use taste-masking polymers and flavorings throughout the thin film, so that any drug released during mouth-dissolution is immediately coated in pleasant tastes. Jacob et al. note that modern ODF design emphasizes aggressive taste masking and palatable mouthfeel to enhance compliance [15]. In any case, by virtue of dissolving on the tongue, ODTs/ODFs demand very thorough flavoring.

Chewable Tablets and Medicated Gums: These must be chewed for release, which means the API is gradually liberated in saliva during mastication. Palatability here relies on either physical isolation of the drug particles (microencapsulation) or blending the drug into a strongly flavored matrix. For example, chewable multivitamins and antihistamines use sweet, fruity or minty bases; any drug cores may be coated or embedded within microcapsules so that the bitter API is not directly tasted [24]. In gums, volatile flavor microcapsules embedded in the gum base release flavor bursts that mask the drug. Some gum formulations employ ion-exchange resin beads (e.g. nicotine gums have the drug sorbed on acidic resin), which release drug slowly only when saliva passes over them, smoothing the taste profile [30]. However, the challenge with chewables is prolonged contact: a leak or incomplete encapsulation means some bitterness can emerge during chewing. Thus chewables/gums typically combine multiple strategies (coated beads, intense flavors, sweeteners) to keep taste acceptable.

Conventional Tablets and Capsules: When swallowed whole, coated tablets and capsules generally bypass the taste buds. Sugar-coatings, polymer film-coatings (cellulose acetate, methacrylate polymers) or enteric-coatings can completely encapsulate the API until the dosage form reaches the stomach [31]. This makes palatability relatively simple if patients swallow the pill intact. The risk is when a patient splits or chews the tablet (sometimes done for dose adjustment). To address this, some tablets are designed as bi-layers or contain sweet or inert subcoats that maintain palatability even if the outer shell cracks. Extended-release matrices (wax or polymer embedding of drug) also retard release so that only minimal drug reaches the mouth if the tablet is partially dissolved [31]. Generally, for swallowable tablets/capsules, palatability concerns center on coating integrity and proper patient instructions rather than flavoring (though tablets are often flavored lightly on the outside).

Specialty and Novel Forms: Many newer oral forms also encounter palatability issues. Dry powders or granules meant for reconstitution must taste acceptable when mixed with water [32]. Effervescent tablets rely on strong fizzy action and

citrus or fruit flavors to mask both API and any "chalky" feel. Mini-tablets (tiny tablets often given to children) minimize taste impact simply by small drug content, and are usually sugar-coated. Orally dissolving mini-tablets follow ODT principles. Even lozenges, films (for buccal drugs), or orally inhaled powders can produce taste sensations and must be formulated with appropriate flavor profile. In every case, the key is that liquid or rapidly-dissolving forms present the greatest taste challenge (since the full dose is available immediately to the taste buds), whereas swallowed forms rely on delaying contact.

Below illustrates examples of bitter APIs and the masking strategy used in marketed products.

Table 1. Examples of bitter APIs and common taste-masking strategies in oral formulations.

Drug (API)	Therapeutic Class	Common Taste-Masking Method
Pseudoephedrine	Decongestant	Sorbed onto ion-exchange resin (Amberlite CG-50) and polymer-coated [32]
Nicotine	Smoking-cessation gum	Complexed with acidic ion-exchange resin in flavored gum base (Nicorette®) [29]
Acetaminophen	Analgesic	Compressed with a molten lipid coating (stearic acid) (lipid barrier) [14]
Dimenhydrinate	Antiemetic	Film-coated with methacrylic polymer (Eudragit) or starch polymer [14]
Ibuprofen	Analgesic/NSAID	Inclusion complex with hydroxypropyl-β-cyclodextrin (forms water-soluble complex) [33]
Morphine HCl	Opioid analgesic	Double-layer coated tablet (inner drug on cellulose core, outer acrylic polymer coat) [34]

Note: These examples (adapted from formulation literature) illustrate how coatings, resin complexes and inclusion complexes can physically prevent bitter APIs from contacting taste buds [33][35].

Taste Masking and Palatability Assessment Techniques

Formulators employ a toolkit of techniques to mask or mitigate unpleasant tastes, which can be grouped as physical (barrier) methods, chemical/complexation methods, and organoleptic (flavor) methods.

Physical Barriers: These include coatings and encapsulation to block drug–saliva contact [22][15]. Tablet or pellet surfaces can be coated with taste-barrier polymers (cellulose derivatives, methacrylate films) so the API is only released after swallowing [22]. Microencapsulation techniques (spray-drying, fluid-bed coating, hot-melt extrusion, coacervation) form microscopic drug particles surrounded by polymer shells [15][36]. For instance, hot-melt extrusion (HME) blends a bitter API with polymer under heat and shear, producing granules in which drug is dispersed in a polymer matrix [15]. Coacervation (phase separation) can coat drug particles in a polymer microcapsule [36]. These microcapsules suspend the drug until reaching the stomach, essentially eliminating mouth taste. Ion-exchange resins are another physical strategy: the drug is bound to a resin (e.g. Amberlite, Indion) as a charged complex and only releases free drug when it encounters counterions in the gut. An example is nicotine gum, where nicotine is held on an acidic resin and released slowly, smoothing its flavor [30].

Chemical/Complexation Methods: This category includes formation of inert complexes or prodrugs. Cyclodextrins (cyclic sugar molecules) are used to form inclusion complexes around small drug molecules, reducing their free concentration in saliva[34]. Adamkiewicz et al. (2023) review

how cyclodextrins trap bitter APIs, preventing them from interacting with taste receptors. Similarly, prodrug approaches (e.g. ester or amino-acid conjugates) can temporarily neutralize a drug's bitter moiety; the prodrug is inert to taste receptors and only converts to the active drug after absorption. Complexation with polyvalent ions (e.g. calcium) or formation of salt forms can also change drug solubility and taste. Inorganic minerals (e.g. magnesium or zinc salts) have been used to form tasteless complexes of some bitter drugs.

Organoleptic (Flavor) Methods: These rely on adding agents that influence taste perception. Sweeteners are ubiquitous: non-caloric sweeteners (sucralose, aspartame), sugar alcohols (xylitol, sorbitol) and natural stevia extracts are used to impart sweetness without significant calories [27]. Flavor extracts (fruit, mint, chocolate, etc.) provide strong pleasant notes that can dominate or mask the drug's flavor. A well-chosen flavor profile can "overshadow" bitterness by providing a more dominant sensory note. Some form manufacturers even employ flavor-releasing microparticles (burst flavor capsules) or effervescence to enhance the sensory experience. Regulators encourage avoiding added sugars in children's medicines, so artificial sweeteners and natural flavors are preferred [27]. Other agents like bitterness blockers (e.g. lactisole for sweet taste, or aldehydes like cinnamaldehyde that suppress bitterness) are explored, though none are universally effective across all drugs. In summary, formulators often combine these methods (for example, a sweetener plus a lipid coating plus an enteric polymer) to achieve an acceptable taste profile.

Palatability Assessment: Once formulations are prepared, their palatability must be assessed. Human sensory evaluation remains the gold standard. Controlled taste panels (usually adults or age-appropriate children) rate taste intensity and hedonic liking under ethical protocols [37][38]. Typical measurements include numerical ratings or hedonic face scales (e.g. 1 = "dislike extremely" to 5 = "like extremely"), visual analog scales, Likert scales and other category scales [37][38]. For example, researchers often ask subjects to rate sweetness, bitterness, aftertaste and overall acceptability using simple numeric or pictorial scales. These tests are designed to minimize bias through randomization and blinding, and standardized "rinse" procedures (e.g. water or cracker between samples). Regulatory guidance (ISO 11136 for acceptability, ISO 3972 for taste) provides best-practice frameworks for designing such trials[37][39]. Risk assessment is critical: low-risk trials (e.g. tasting commercial products with no new APIs) proceed under simple protocols, whereas testing unapproved drugs requires full clinical oversight [37][39].

Table of Palatability Scales: A variety of sensory scales are used (see Table 2). Common approaches include hedonic face scales for young children, numeric VAS for older patients, and verbal categories ("no taste" to "extremely bitter"). Choice of scale depends on age and context. For instance, a 5-point facial hedonic scale is standard in pediatric studies [37]. Trained analytical panels may use highly calibrated scales to quantify exact bitterness intensity, whereas consumer panels focus on overall liking and acceptability.

Instrumental and In Silico Methods: To complement human tests, instrumental techniques like electronic tongues (e-tongues) and computational models are increasingly used [3][4]. E-tongues are sensor arrays (potentiometric, voltammetric or impedance-based) designed to mimic human taste reception. Early studies (Legin et al. 2004) showed that potentiometric e-tongues

could distinguish substances by taste and even quantitatively predict perceived bitterness [3]. After calibration, e-tongues were able to predict the "apparent quinine concentration" (a measure of bitterness) in mixtures with sweeteners [3]. They have also successfully classified formulations with different levels of sweetener or flavor, correlating well with small human panels of taste testers. E-tongues offer high reproducibility, rapid throughput and no ethical issues (no human subjects), making them attractive screening tools in early development [40]. However, they have drawbacks: sensor drift over time, limited availability of sensors for every taste quality, and the fact that regulatory authorities still consider them supplemental. Thus, e-tongues serve as a cost-effective pre-screening step, with final product decisions relying on human sensory confirmation [41][40].

Computational predictions are emerging in palatability design. Large databases of molecular tastants now allow machine-learning models to predict taste from structure. For example, a recent chemical-language transformer model (FART) achieved >91% accuracy in classifying compounds as sweet, bitter, sour or umami based solely on structure[5]. Another AI platform ("TastePepAI") has even designed novel sweet/umami peptide motifs, which were experimentally validated by e-tongue tests to have the intended flavors [42]. These in silico methods promise to flag problematic APIs early and suggest new flavoring excipients, though they are still under development.

In practice, palatability assessment follows a risk-based workflow [39][43]. Simple screening (e.g. "rinse-and-spit" tests of known drugs) can be done with naïve adult volunteers. Higher-risk formulations (new molecules or pediatrics) require thorough risk assessment: investigators must ensure volunteer safety (considering API toxicity, dosing, inclusion/exclusion criteria) before proceeding [39][43]. Analytical taste panels of trained assessors may first profile specific taste attributes, followed by broader hedonic panels of target patients or caregivers to gauge liking. Through a combination of human sensory data, instrumental measurements and computational insight, developers can iteratively refine a formulation's taste profile.

Evaluation of Palatability

Evaluating palatability is a multi-step process involving both human and instrumental methods, each with distinct roles:

Human Sensory Panels: As emphasized above, human taste tests are the ultimate arbiter of palatability [39]. Panels may be split into analytical (trained) vs. consumer (naïve) groups. Analytical panels use precise sensory vocabulary and scales to profile taste and aftertaste, whereas consumer panels (including children or the elderly) provide overall acceptability ratings. Clinical trials often include palatability endpoints; e.g. pediatric trials may ask caregivers or children to rate medication acceptability on a validated face scale. Regulatory bodies now expect some sensory data for pediatric approvals. According to Clapham et al., only sensory studies in human volunteers can definitively confirm that a formulation is non-aversive [39]. Indeed, despite in vitro advances, "it is only possible to be sure… by undertaking sensory assessments in human volunteers" [39]. Human testing must follow ethical guidelines: informed consent, blinded crossover designs (often "rinse-and-spit"), appropriate washout between samples, etc. [37][38]. Post-marketing, patient-reported outcomes (questionnaires, diaries) may also capture palatability issues. Overall, while

laborious and expensive, human panels provide direct evidence of real-world acceptability.

Instrumental Sensor Systems: E-tongues and related chemical sensors provide objective, reproducible flavor assessments. As noted, potentiometric multichannel sensor arrays correlate well with human bitterness and sweetness ratings [3][40]. Newer versions use quartz crystal microbalances, biosensors or impedance arrays for finer discrimination. Some devices can approximate mouthfeel (e.g. flow-cell viscosity sensors) or smell (e-noses), but taste remains primary. In a development setting, a formulation scientist might run dozens of candidate formulations through an e-tongue to rank their bitterness or sweetness profiles before any human testing [3][40]. However, since these devices sense chemical features, they may not capture the full holistic experience (aroma, trigeminal sensations) that a person would. Thus, instrumental data are usually calibrated to human panel data. For instance, an e-tongue might give an "apparent quinine" value for a syrup, which is then mapped to expected perceived bitterness. Such quantitative tools accelerate screening but do not replace human panels [40][38].

Clinical Correlation: Ultimately, the goal of evaluation is to link palatability to outcomes. Ideally, palatability scores (e.g. average liking rating) would correlate with adherence or dropout rates. In practice, such data are sparse and complicated by many factors. The systematic review by Squires et al. found that palatability is "often assessed" in pediatric trials (usually by simple visual scales), but rigorous evidence linking those scores to actual compliance is limited [44]. Still, empirical correlations exist – one pediatric antibiotic study found that better-tasting alternatives dramatically increased course completion rates [2][1]. Clinical trial designs increasingly include acceptability end-points (e.g. completion of therapy, patient/caregiver preference surveys) alongside pharmacokinetic outcomes. By combining palatability assessment with adherence monitoring, manufacturers can evaluate the real-world impact of their taste-masking efforts.

Regulatory and Practical Considerations: Sensory evaluations must also satisfy regulators. Agencies in Europe and the US recognize taste as a "major barrier" to pediatric treatment and have begun incorporating palatability into guidelines. For example, the EMA's pediatric guidance encourages characterizing taste in development, and the FDA has guidance on safely conducting taste studies with children. However, there is no single standardized palatability test in the pharmacopeia; companies often follow ISO standards from the food industry or adapt schemes from literature [39][44]. Key challenges include the lack of validated scales for very young children (who cannot verbalize ratings easily) and the ethics of repeatedly tasting experimental drugs. As a result, some studies resort to caregiver assessments or surrogate endpoints. Recent proposals (e.g. by EuPFI) suggest stepwise testing: initial technical panels, followed by limited safety-graded human trials under clinical supervision [39].

In summary, palatability evaluation integrates: (a) psychophysical taste panels (primary data on liking/bitterness), (b) instrumental assays (rapid, objective profiling) and (c) clinical observations (adherence, acceptability endpoints) [38][39]. Each method has strengths and limitations, so an integrated approach is needed. Emerging tools (e.g. animal taste assays, high-throughput electronic sensors, and in silico modeling) aim to reduce reliance on human testers, but for now the human tongue is the definitive "instrument."

Impact of Palatability on Patient Compliance

The link between taste and compliance is well-documented, particularly in vulnerable populations. Poor palatability leads patients (or caregivers) to skip doses, alter regimens, or abandon treatment altogether. In pediatrics, where syrups and chewables are common, taste is frequently the single biggest reason for non-adherence [7][1]. For example, Baguley et al. report that bitter antibiotics like flucloxacillin are so unpalatable that clinicians warn to "taste-test" syrups before prescribing them to children [7]. In a large Israeli study of 546 children on antibiotics, 56% of those given cefuroxime axetil (a very bitter drug) expressed resistance, and only 67% completed the full course, compared with 85% completion for the mild-tasting cefaclor [2]. Similar patterns appear across studies: palatability issues in HIV and malaria therapies (in resource-limited settings) contribute to incomplete dosing and the risk of resistance. In Ranmal et al.'s recent scoping review, 64% of pediatric medication studies reported outright rejection (spitting out or refusing doses), and 27% reported adherence problems attributable to poor taste [1]. These avoidances often lead caregivers to modify the treatment (mixing drugs into foods, splitting tablets, or substituting second-best drugs) – practices that can compromise efficacy.

Adults, too, prefer palatable medications; even elderly patients often favor flavored or easy-to-swallow forms. Dysphagia in geriatrics sometimes leads to crushing pills (exposing taste), and any bitterness can deter use. For chronic conditions (epilepsy, hypertension, depression, etc.), the risk is particularly high: one review found that over a quarter of studies in such contexts linked taste issues to non-adherence [45]. The consequences are serious: missed doses lead to treatment failure (e.g. viral rebound in HIV, seizure relapse) and wastage of therapy. In contrast, medications engineered to taste acceptable have measurably better outcomes. Although clinical trials rarely randomize on "good taste vs. bad taste," patient surveys consistently rank "bad taste" among the top reasons for dissatisfaction. Regulators now often request palatability data in pediatric investigational plans.

Nevertheless, it is worth noting that solid evidence directly correlating palatability scores with compliance is still emerging. Squires et al. found that most pediatric studies use simple unvalidated scales and don't systematically track adherence, so data are limited [44]. However, the preponderance of reports (questionnaires, clinical anecdotes, caregiver feedback) points to taste as a major driver of real-world use. The hidden "cost" of ignoring taste – treatment failure, extra doctor visits, and in worst cases drug resistance – is well-recognized in global health circles [7]. Ultimately, ensuring good palatability is not just about patient comfort; it is integral to therapeutic effectiveness and public health.

Recent Advances & Future Perspectives

Technology is rapidly opening new frontiers in palatability science. Key areas of innovation include:

In Silico Taste Prediction: AI and big data are transforming how we anticipate taste problems. With large public datasets of molecular tastants available, machine learning models now predict flavor from chemical structure alone [5]. For example, a recent transformer-based model (FART) achieved over 91% accuracy in classifying compounds as sweet, bitter, sour or umami [5]. Such tools can screen candidate APIs or excipients during drug design, flagging bitterness issues before any formulation work begins. Furthermore, algorithms can suggest

molecular modifications or potential sweetener partners to modulate taste. This predictive approach is analogous to ADMET prediction – taste is simply a new "ADMET" parameter in silico.

Biologically-Inspired and AI-Designed Flavor Compounds: Beyond prediction, AI is being used to create entirely new taste agents. Recently, a platform called "TastePepAI" employed deep learning to design peptide-based flavors – short amino-acid sequences that are sweet or umami-tasting. Lab testing (via electronic tongue) confirmed that dozens of the AI-generated peptides had the intended taste profiles [42]. This suggests a future where novel natural-like sweeteners, bitter blockers, or umami enhancers are custom-designed for formulation needs. Nature itself provides templates: thousands of taste-active peptides exist (e.g. miraculin, pentadin) that might be mimicked or improved by computation [42]. Such advances could yield flavoring excipients with higher potency, stability and safety than current options.

3D Printing and Personalized Dosage Forms: Additive manufacturing is revolutionizing how we deliver medicines. 3D printing allows custom geometries, multi-layer structures and multi-drug combinations in a single tablet [46][47]. Critically for taste, a tablet can be printed with a bitter API confined to an inner core and surrounded by an outer layer of sweet matrix or dissolvable film [29][47]. Printers can also embed microcapsules of flavor or sweetener in precise patterns. For example, one clinical trial (FabRx Printlets) produced personalized chewable tablets for a metabolic disease by 3D printing tailored doses with child-friendly flavors, achieving good acceptability [47]. In effect, 3D printing turns medication into a bespoke product, where each patient can even choose from a menu of flavors. AI-driven design tools will further optimize printability, layer thickness, and flavor distribution. Although still largely in R&D, 3D-printed formulations represent a glimpse of patient-centric pharmacy, where palatability is engineered from the molecule up.

Advanced Sensors and In Vitro Models: Next-generation bio-sensor technologies are under development. Some researchers are working on cell-based bioassays that use taste-receptor-expressing cells or organoids to detect bitterness [48]. Biosensors and nanomaterials (surface acoustic wave devices, bioelectronic tongues) promise higher sensitivity and the ability to profile multi-modal sensations (taste + aroma). Additionally, efforts to use taste-modified animals (e.g. catfish with suppressed salinity sensors) have been explored, although ethical considerations apply [48]. These approaches may eventually reduce the need for large human panels, but they remain complementary at present.

Novel Excipients and Delivery Vectors: Researchers continue to seek new materials specifically for taste masking. For example, functionalized cyclodextrins, ionomers, self-assembling lipids and pH-responsive polymers are being tailored for drug encapsulation. Lipid-based carriers (micelles, liposomes) can also entrap hydrophobic bitter drugs. Some groups are engineering taste-modulating enzymes or proteins that can be co-administered to neutralize bitter molecules in saliva. In pharmaceuticals, using such biologicals is challenging, but the concept is being tested in the food industry.

Personalized and Adaptive Therapies: In the future, one might imagine on-demand customization of flavors per patient. Mobile apps already survey patient flavor preferences; combined with rapid manufacturing, a pharmacy could theoretically match a child's favorite fruit

flavor to an antibiotic dose prepared on-site. Such personalization is still speculative, but the groundwork is being laid by AI and digital manufacturing.

In short, the trajectory is towards preemptive palatability engineering: using computational tools to predict issues, employing advanced materials to mask tastes at the molecular level, and leveraging manufacturing technologies to customize dosage forms (including flavor design). These advances hold the promise of making "Yuck-free" pills a reality across all age groups.

Challenges and Limitations

Despite progress, significant challenges remain in palatability science.

Lack of Standardization: There is no universally accepted metric for palatability. Different studies use different scales (numerical, faces, categories), often invalidated [44]. This makes comparisons across studies difficult. The pediatric literature often relies on caregiver or patient-reported "acceptability" without consistent methodology. Squires et al. found that virtually all trials used bespoke, invalidated scales, and none had a standard analysis plan [44]. Without standard norms, even rating what "4" on a 5-point scale means can vary. The field would benefit from an agreed-upon palatability scale (analogous to a pain scale) and statistical conventions for analysis.

Ethical and Safety Constraints: Human testing of taste has inherent limits. New chemical entities, or formulations containing potent APIs, cannot be directly tasted in early development due to safety. Even for marketed products, exposing children to a novel flavor or formulation requires careful IRB review. Risk assessment procedures are needed to ensure volunteer safety [39][43]. As one review notes, volunteers may experience "multiple difficulties" in taste trials (e.g. heightened gag reflex, allergic reactions, fatigue) [38]. These constraints can limit when and how taste assessment can be done, potentially delaying feedback in development.

Subjectivity and Variability: Human taste perception is subjective and variable. Genetic differences (supertasters vs. non-tasters) mean that the same formulation might be rated very differently by different people [38]. Factors like hunger, fatigue, or concurrent medications can alter results. Children's reports can be inconsistent or influenced by their mood. These sources of variability can introduce noise in the data. Large panel sizes can mitigate this, but at increased cost. Trained panels reduce variability but may not represent target patient responses.

Instrument Limitations: Electronic tongues and other sensors have limitations. Sensor drift and cross-sensitivity require frequent recalibration. A single e-tongue unit cannot yet fully capture the multi-sensory experience of taste + aroma + texture. Moreover, regulatory agencies have limited experience with instrumental palatability data, so such data are often used only as supportive screening. There is also a practical limitation: an e-tongue might require relatively large sample volumes and specific pH conditions (e.g. fairly neutral solutions), which may not mimic real-use conditions.

Formulation Trade-offs: Some taste-masking strategies introduce other issues. For instance, coating a tablet might delay drug release if done improperly, affecting bioavailability. Adding high concentrations of sweeteners could raise concerns about caloric load or dental health (especially in children). Certain polymers or flavors may cause allergic reactions or stability problems. There is also a potential label-generic discrepancy: patients might recognize or prefer the taste of a brand-name

syrup but find a generic version (different dye or flavor) unacceptable.

Evidence Gaps: While many assume "good taste = better adherence," rigorous clinical data are still emerging. As noted, systematic reviews call for more studies linking palatability tests to actual patient behavior [44]. There is a chicken-and-egg problem: companies seldom publish negative palatability results, so literature can be biased. More real-world studies are needed to quantify how much improvement in taste actually translates into improved health outcomes.

In summary, technical and practical hurdles – from methodological inconsistency to ethical limits on testing – constrain palatability research. Addressing these will require cross-disciplinary collaboration: sensory scientists, formulation chemists, clinicians and regulators working together to define best practices and standards.

CONCLUSION

As this review has shown, a comprehensive approach—one that integrates a deep understanding of drug chemistry, smart formulation design, and rigorous sensory evaluation—is essential to successfully tackle palatability challenges.

While traditional techniques such as sweeteners, functional coatings, encapsulation, and chemical complexation remain the backbone of taste masking, they are increasingly augmented by cutting-edge tools. These include electronic tongues, molecular taste prediction algorithms, 3D-printed multilayer tablets, and AI-designed flavor excipients. Moving forward, establishing early collaboration with patients and caregivers, developing better palatability metrics, and incorporating sensory testing at the very outset of drug development will ensure that taste issues are never treated as an afterthought.

Looking ahead, the pharmaceutical field is rapidly moving toward predictive and patient-tailored solutions, such as screening out bitter compounds in silico, formulating on-demand medications with adjustable flavors, and discovering novel taste modulators. Although technical, ethical, and regulatory challenges remain, the momentum is undeniable: effective medications that are also pleasant to take are becoming the industry standard. By prioritizing these advancements, pharmaceutical development aligns more closely with real-world patient needs, ultimately promising higher compliance and superior therapeutic outcomes.

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