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PREDICTING PEDIATRIC LIQUID PALATABILITY USING SWEETENERS, BITTERNESS, VISCOSITY, AND ACCEPTABILITY DATA

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ABSTRACT

Pediatric adherence is strongly shaped by whether a child can tolerate the taste, texture, and aftertaste of an oral medicine. Liquid formulations are especially complex because bitterness, sweetness, viscosity, and aroma are experienced together rather than as isolated attributes. Current palatability development often depends on expert judgment, small sensory panels, and iterative reformulation. These approaches can identify unacceptable products, but they do not reliably predict how a planned change in sweetener, bitterness masking, or viscosity would affect future child acceptability. This predictive modeling article proposes a machine learning framework for estimating pediatric liquid palatability from sweetener characteristics, API bitterness, viscosity, and prior acceptability data. The intended outputs are a predicted acceptability score, a rejection-risk indication, and interpretable formulation guidance. A gradient-boosted regression and classification framework is proposed for curated formulation records containing sweetener identity and concentration, electronic-tongue or sensory bitterness measurements, rheological descriptors, and historical pediatric or caregiver acceptability observations. The model is conceptual and is intended to guide study design rather than report experimental findings. Conceptually, the model could identify whether bitterness intensity, sweetener potency, sweetener concentration, viscosity, or their interactions are most responsible for a predicted palatability limitation. It would be expected to support virtual screening of formulation variants before pediatric panel testing. Predictive palatability modeling could reduce reliance on late-stage trial-and-error in pediatric liquid formulation development. A standardized dataset linking objective measurements with human acceptability outcomes would be essential for reliable implementation.

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Introduction

Palatability is a central determinant of whether children will accept and continue oral pharmacotherapy, particularly when treatment requires repeated dosing over days or months [1]. Pediatric liquid medicines are often selected because they are flexible and easier to administer than solid forms, yet the same liquid format exposes children directly to the bitterness of the active pharmaceutical ingredient and to the mouthfeel of the vehicle [2]. Studies of pediatric medicines have repeatedly shown that acceptability depends not only on taste but also on appearance, smell, texture, swallowing comfort, and the context in which the medicine is administered [3]. For bitter APIs, the challenge is not merely to add sweetness, but to balance bitterness suppression, aftertaste management, and age-appropriate sensory expectations [4].

Current pediatric formulation development commonly relies on expert judgment, excipient heuristics, electronic-tongue screening, and limited human acceptability panels [5]. These methods are valuable but costly and difficult to standardize, especially when studies differ in rating scales, age groups, dosing context, and caregiver involvement [6]. Taste-masking technologies such as cyclodextrin complexation, multiparticulate coating, and ion-exchange approaches may improve sensory performance, but their effects are formulation-specific and difficult to generalize without structured data [7]. As a result, a formulation that appears acceptable during early development can still encounter late-stage palatability risk if bitterness, sweetness, and texture have not been evaluated as interacting variables [8].

The increasing availability of electronic tongues offers a route toward objective bitterness measurement, particularly when pediatric sensory testing is impractical or ethically constrained [9]. Electronic tongues can generate sensor response patterns

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that distinguish bitter formulations or quantify changes after taste masking, but the relationship between sensor output and human acceptability remains dependent on product type, excipients, and the reference method used [10]. In parallel, machine learning has matured in food sensory prediction, where tabular formulation, physicochemical, and sensory descriptors are increasingly used to estimate flavor, texture, and consumer response [11]. These developments create the basis for a pharmaceutical palatability model that connects objective bitterness fingerprints with historical acceptability data rather than treating each formulation study as an isolated event [12].

This article proposes a predictive model for pediatric liquid palatability that uses sweetener type and concentration, API bitterness intensity, viscosity measurements, and historical acceptability outcomes as core inputs [13]. The model is not intended to replace pediatric acceptability studies, but to prioritize the most promising formulation candidates before human evaluation [14]. By encoding sweetness potency, electronic-tongue distance, panel bitterness scores, viscosity at oral-processing-relevant shear conditions, and taste-masking excipient levels, the model could estimate an acceptability score and flag formulations with elevated rejection risk [15]. In this way, predictive palatability modeling would support formulation scientists in choosing rational sweetener and texturizing strategies while preserving the need for confirmatory sensory evaluation [16].

Background

Determinants of Palatability in Pediatric Liquids

Pediatric liquid palatability reflects an integrated sensory response involving sweet taste, bitter taste, aroma, aftertaste, mouth coating, viscosity, grittiness, and ease of swallowing [2]. Children may respond differently from adults because sensory preferences, aversion to bitterness, and the ability to describe sensations change with development, which complicates the use of adult panels as direct surrogates for pediatric acceptability [4]. Color and visual expectations may also influence willingness to take a medicine, especially when a child associates a particular appearance with pleasant or unpleasant flavors [17]. Therefore, a predictive model should treat palatability as a multidimensional construct rather than a simple function of API bitterness alone [1].

Sweeteners and Taste-Masking Excipients

Sweeteners such as sucrose, sucralose, aspartame, and steviol glycosides differ in sweetness potency, onset, duration, lingering aftertaste, and interaction with bitter compounds [18]. Psychophysical studies comparing multiple sweeteners show that perceived sweetness does not increase uniformly across sweeteners or concentrations, so a model should encode relative sweetness and temporal profile rather than only the mass of sweetener added [15]. Temporal check-all-that-apply methods further show that sweetness and side tastes evolve over time, which is relevant for pediatric liquids where aftertaste may drive refusal after swallowing [19]. Taste-masking excipients such as cyclodextrins and multiparticulate systems can reduce bitterness exposure through complexation or physical separation, so their concentrations should be represented as formulation features alongside sweetener variables [7].

Figure 1 summarizes how sweetener identity, concentration-dependent psychophysical behavior, temporal sensory evolution, and taste-masking excipients jointly shape palatability-relevant formulation features for pediatric liquid medicines.

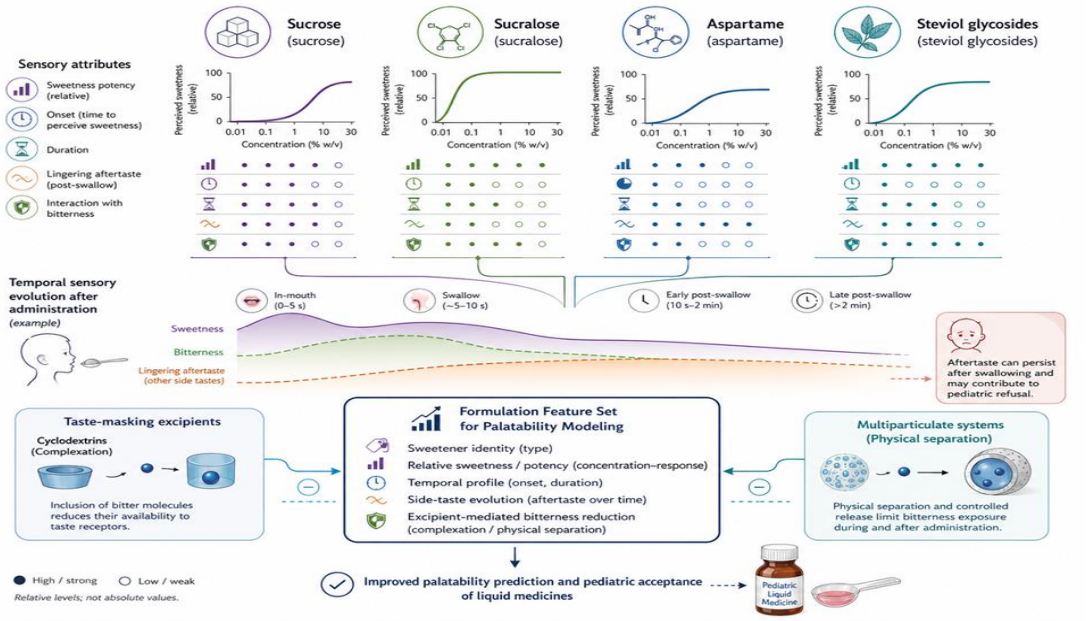

Figure 1. Representation of Sweetener Sensory Profiles and Taste-Masking Excipients as Formulation Features in Pediatric Liquids

Measuring Bitterness: Electronic Tongues and Sensory Panels

Electronic tongues provide objective sensor patterns that can be used to compare bitterness fingerprints across APIs, formulations, and taste-masked variants [10]. In pharmaceutical development, electronic-tongue methods have been applied to detect taste-masking effects and to support formulation decisions when human taste testing is limited [20]. However, qualification of electronic tongues remains challenging because sensor response does not automatically translate into pediatric acceptability, and correlation with human panels depends on calibration, reference compounds, and product matrix [9]. Human sensory panels remain essential for anchoring bitterness scores and acceptability ratings, but pediatric panel design must account for developmental ability, ethical limits, and measurement burden [6].

Viscosity and Its Impact on Acceptability

Viscosity changes the mouthfeel, flow, coating behavior, and swallowability of liquid medicines, and these physical sensations can either improve or reduce acceptability depending on age and formulation context [21]. Liquids thickened for swallowing safety show that rheological behavior and standardized texture categories can be quantified, but pediatric medicines must also consider whether increased thickness prolongs contact with bitter tastants [22]. Viscosity may modulate taste intensity by changing oral residence time and flavor release, which means it should be modeled as an interacting feature rather than as a simple acceptability modifier [23]. For pediatric formulations, age-appropriate viscosity should therefore be considered jointly with sweetness and bitterness rather than optimized after taste masking is complete.

Machine Learning in Sensory and Formulation Science

Machine learning has been increasingly used to predict food flavor, texture, and sensory quality from ingredient, chemical, and physicochemical descriptors [11]. Reviews of food sensory modeling indicate that random forests, gradient-boosted models, neural networks, and partial least squares methods can support prediction when data are structured but heterogeneous [16]. Multiobjective taste prediction also shows that computational models can estimate multiple taste sensations simultaneously, which is relevant to pediatric liquids where sweetness, bitterness, and aftertaste coexist [12]. In pharmaceutical palatability, early work has begun to connect human taste panel data with model training, but the field still requires standardized features, interpretable outputs, and careful validation against pediatric acceptability outcomes [13].

Model Development Overview

High-Level Predictive Pipeline

The proposed pipeline begins with a candidate liquid formulation described by sweetener composition, bitterness measurement, viscosity profile, and available sensory or acceptability metadata [13]. These inputs would be transformed into a structured feature vector that can be processed by a supervised model to estimate a continuous or ordinal acceptability score and a rejection-risk category [3]. Because pediatric acceptability studies use different instruments, including hedonic scales, facial-expression methods, caregiver reports, and observed refusal, the pipeline should standardize outcomes while retaining information about the original assessment method [6]. An uncertainty estimate would be expected to help identify cases where the formulation lies outside the experience represented in the training data [11].

Figure 2 illustrates the proposed sensory-evidence-to-formulation-guidance architecture for predicting pediatric liquid palatability from sweetener, bitterness, viscosity, acceptability, and study-context data.

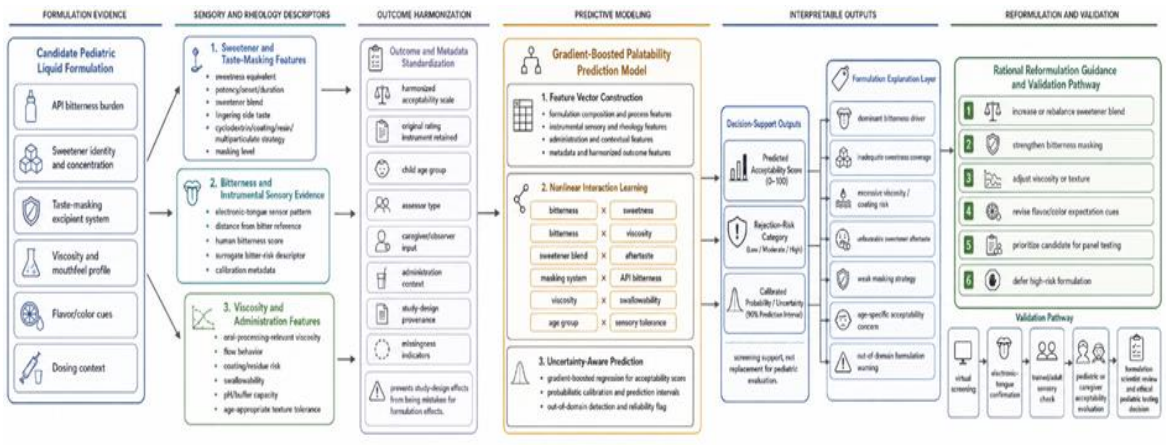

Figure 2. Interpretable Predictive Architecture for Pediatric Liquid Palatability Using Sweeteners, Bitterness, Viscosity, and Acceptability Evidence

Core Input Features

Core features would include sweetener identity, concentration, sweetness equivalent relative to sucrose, and temporal sweetness characteristics when available [15]. API bitterness would be represented using electronic-tongue distance from

reference formulations, normalized panel bitterness scores, or surrogate bitterness predictions when experimental measurements are unavailable [9]. Viscosity should be encoded at a reference shear condition relevant to oral handling, while optional descriptors such as pH, buffer capacity, aroma type, color, and taste-masking excipient concentration could capture additional formulation signals [17]. This feature design allows the model to represent both direct sensory drivers and formulation interventions such as cyclodextrin complexation, coating, or multiparticulate taste masking [24].

Design Principles

The model should be capable of handling sweetener mixtures because pediatric liquids often use combined sweeteners to balance potency, onset, and aftertaste [19]. It should remain robust when electronic-tongue data are missing, because historical acceptability records may contain human panel outcomes without instrumental bitterness fingerprints [5]. Interpretability is essential because formulation scientists need to understand whether a prediction is driven by bitterness, inadequate sweetness, excessive viscosity, or an unfavorable combination of features [23]. Generalization across APIs and age groups should be treated as a design objective, since children, adults, and expert assessors may differ in bitterness aversion and palatability judgments [4].

Data Sources and Feature Engineering

Assembling a Palatability Dataset

A palatability dataset would be assembled from published pediatric acceptability studies, internal formulation development records, electronic-tongue databases, and structured sensory assessments of liquid medicines [1]. Published work on pediatric acceptability provides examples of heterogeneous outcome capture, including direct child response, caregiver assessment, and clinical-administration observations [6]. Studies of specific pediatric formulations, such as valaciclovir, carbocysteine, omeprazole, and enalapril products, illustrate the range of sensory and acceptability evidence that could be curated for model training [14]. Because scales and study designs differ, hedonic scores should be mapped to a common conceptual acceptability framework while preserving study-level metadata to avoid overinterpreting non-equivalent measurements [25].

Encoding Sweetener and Bitterness Features

Sweetener blends would be encoded using both categorical identity and quantitative descriptors, including concentration, sweetness potency relative to sucrose, and temporal sweetness profile where available [18]. The model should distinguish between sweetness intensity and bitterness masking, because a sweetener may increase perceived sweetness without fully suppressing bitter aftertaste [19]. Bitterness could be represented as an electronic-tongue distance, sensor response pattern, normalized human bitterness score, or a formulation-level bitter-risk descriptor derived from available API information [20]. Taste-masking excipients such as cyclodextrins, coatings, resins, and multiparticulate approaches should be encoded as mechanistic features because they may reduce free bitter tastant exposure rather than simply add a competing taste [8].

Table 1 organizes the proposed input space according to each feature domain's sensory meaning, modeling function, interaction logic, and practical formulation implication.

Table 1. Feature Domains, Sensory Meaning, and Modeling Role in Pediatric Liquid Palatability Prediction

Feature domain	Representative variables	Sensory or formulation meaning	Modeling role	Key interaction to examine	Practical formulation implication
Sweetener system	Sweetener identity, concentration, sucrose-equivalent sweetness, blend composition, onset, duration, lingering side taste	Captures the intensity and temporal profile of perceived sweetness rather than only excipient mass	Core predictor of sweetness coverage and aftertaste risk	Sweetener potency × API bitterness intensity	Helps determine whether additional sweetness, a different sweetener, or a blend adjustment is more rational than simply increasing concentration
API bitterness burden	Electronic-tongue distance, human bitterness score, bitter-risk descriptor, bitterness persistence	Represents the sensory challenge that must be masked or balanced	Core predictor of rejection risk and masking demand	Bitterness intensity × masking strategy	Identifies formulations where sweetness alone is unlikely to overcome bitter exposure
Taste-masking strategy	Cyclodextrin level, coating system, ion-exchange resin, multiparticulate design, complexation approach	Describes mechanisms that reduce exposure to free bitter tastant	Mechanistic feature explaining why similar APIs may differ in perceived bitterness	Masking system × API bitterness × viscosity	Supports selection of masking approaches that address bitter release rather than only taste competition
Viscosity and rheology	Viscosity at oral-processing-relevant shear, flow behavior, coating tendency, residue risk, swallowability category	Captures mouthfeel, oral residence time, swallowing comfort, and potential bitter aftertaste prolongation	Interaction feature linking physical texture with taste perception and administration burden	Viscosity × bitterness exposure; viscosity × child age group	Helps avoid formulations that improve texture or suspension stability but increase mouth coating or refusal risk

Physicochemical context	pH, buffer capacity, ionic strength, excipient matrix, API solubility indicators	Influences ionization, taste perception, release behavior, and masking performance	Secondary explanatory feature and confounding-control variable	pH × bitterness; pH × masking excipient	Prevents sensory effects from being interpreted without considering matrix chemistry
Sensory expectation cues	Aroma type, flavor category, color, appearance, dose volume, administration context	Shapes willingness to accept the medicine before and during dosing	Optional contextual predictor of acceptability variation	Flavor/color cue × age group; aroma × bitterness	Guides non-active sensory modifications when taste chemistry alone does not explain refusal
Acceptability outcome	Hedonic rating, facial scale, caregiver report, observed refusal, willingness-to-take, repeat-dose adherence indicator	Provides the target variable for prediction but may vary by instrument	Regression or classification endpoint after harmonization	Outcome instrument × assessor type	Requires careful standardization so that the model learns palatability rather than study-method artifacts
Population and study metadata	Age group, assessor type, clinical context, dosing frequency, study setting, respondent role	Captures developmental and methodological differences in palatability assessment	Stratification, covariate adjustment, or subgroup modeling feature	Age group × viscosity; assessor type × bitterness rating	Supports age-specific interpretation and reduces bias from mixing child, caregiver, adult, and expert assessments

Viscosity and Other Physicochemical Features

Viscosity features should be derived from rheological measurements that reflect oral processing rather than from a single uncontrolled flow observation [21]. In pediatric liquids, a formulation that is too thin may be easy to swallow but may expose bitterness rapidly, while a formulation that is too viscous may increase coating, residue, or refusal risk [22]. pH and buffer capacity may also influence ionization, taste perception, and the effectiveness of bitterness masking, so they should be included when available as secondary physicochemical descriptors [7]. Flavoring type, color, and dosage form context can be represented as optional categorical features because sensory expectation and administration setting may affect acceptability beyond chemical taste alone [17].

Predictive Model Architecture

Model Choice – Gradient-Boosted Trees

Gradient-boosted tree models are a suitable conceptual choice for pediatric palatability prediction because they can represent nonlinear interactions among sweetness, bitterness, viscosity, and excipient composition in tabular formulation data [16]. Compared with purely linear methods, a boosted tree could learn that increasing sweetness may be helpful within one bitterness range but less influential when bitterness exceeds the practical masking capacity of the selected excipient system [12]. Such a model would also be compatible with interpretability workflows that rank the relative contribution of sweetener features, electronic-tongue signals, and rheological descriptors to a prediction [23]. The model should be evaluated conceptually against alternative approaches, including random forests, partial least squares, and neural networks, without assuming that any architecture is universally optimal for all pediatric formulation datasets [11].

Input Feature Vector and Pre-processing

The input feature vector would combine normalized continuous variables, such as sweetener concentration, sweetness equivalent, bitterness score, viscosity, and pH, with categorical encodings for sweetener type, API class, flavoring, color, and taste-masking strategy [15]. Missing electronic-tongue data could be handled through model-native missingness treatment or through a surrogate bitterness estimate, while the missingness indicator itself may carry useful information about data provenance [9]. Panel-derived outcomes should be pre-processed with attention to the original rating scale, child age group, caregiver involvement, and whether the outcome reflects immediate taste, aftertaste, swallowing, or overall willingness to take the dose [6]. These steps would help reduce the risk that the model confuses true formulation effects with differences in study design or sensory measurement method [1].

Output: Acceptability Score and Classification

The model would output a predicted acceptability score on a harmonized continuous or ordinal scale, together with a conceptual acceptable or unacceptable classification for formulation decision support [3]. A calibrated probability of acceptability could help formulators compare candidate liquids without treating the prediction as a definitive substitute for pediatric or caregiver evaluation [2]. For example, a formulation with strong sweetener potency but high viscosity might be flagged for textural reformulation, whereas a low-viscosity formulation with a large bitterness signal might be prioritized for taste-masking intervention [26]. The output should therefore be designed as a formulation-guidance tool that supports rational screening before confirmatory human acceptability work [27].

Handling Sensory Data Variability and Panel Reliability

Accounting for Inter-Panel Variability

Inter-panel variability is a major concern because pediatric acceptability data may come from children, caregivers, trained adults, naïve adults, or expert sensory assessors, and these groups can respond differently to bitterness and overall medicine acceptability [4]. A model could incorporate panel-descriptive features such as age group, assessor type, study location, administration context, and whether the rating was child-reported, caregiver-reported, or observer-recorded [6]. The reliability of each outcome should be interpreted in relation to the assessment instrument, because acceptability questionnaires, hedonic scales, and observed refusal measures capture related but not identical constructs [1]. By encoding these sources of variation, the model would be expected to reduce systematic bias when learning from heterogeneous palatability studies [2].

Dealing with Small and Imbalanced Datasets

Pediatric palatability datasets are likely to be small, imbalanced, and clustered by API or formulation platform, so evaluation and training should avoid treating near-duplicate formulations as fully independent observations [13]. Cross-validation should respect formulation families and API identity, because a model that only interpolates within one bitter compound may not generalize to a chemically different API [11]. When acceptable formulations are overrepresented because failed prototypes are not always published, the model should explicitly account for publication and selection bias rather than assuming that the observed dataset reflects the full formulation space [3]. Synthetic sampling or augmentation may be explored only when grounded in known sensory relationships, such as sweetness potency or temporal side-taste behavior, rather than used to invent unsupported pediatric outcomes [19].

Incorporating E-Tongue Data as Surrogate Markers

Electronic-tongue responses can serve as surrogate bitterness markers for formulations that have not yet undergone pediatric or caregiver acceptability assessment [10]. The model could learn a mapping between sensor patterns, human bitterness scores, and acceptability outcomes, while recognizing that the electronic tongue captures only part of the sensory experience [9]. Taste-masked levetiracetam formulations and cyclodextrin-based bitterness reduction studies illustrate how instrumental signals may support formulation comparisons before human testing [20, 26]. However, these surrogate markers should be interpreted as decision-support features rather than replacements for human acceptability data, because aroma, aftertaste, swallowing comfort, and child-specific aversion may remain outside the electronic-tongue signal [5].

Model Interpretability and Formulation Guidance

Explaining Acceptability Predictions to Formulators

Interpretable model outputs are essential because formulation scientists need to know which modifiable variable is responsible for a predicted acceptability concern [23]. Feature-attribution methods could rank bitterness intensity, sweetener concentration, sweetness equivalent, viscosity, taste-masking excipient level, flavoring type, and color according to their contribution to the predicted score [17]. A poorly predicted formulation might be explained by excessive viscosity even when sweetness is high, or by persistent bitterness that is not sufficiently reduced by the selected masking excipient [7]. Such explanations would make the model more useful than a black-box acceptability estimate, especially when reformulation options include changing sweetener blend, adding complexation, adjusting rheology, or modifying flavor cues [8].

From Prediction to Optimal Formulation

The model could support virtual screening by estimating how alternative sweetener–viscosity combinations might affect expected acceptability before producing every candidate formulation [16]. For example, sweetness data from consumer studies can inform how different sweeteners and concentrations are encoded, while viscosity and swallowability evidence can constrain predictions to physically plausible pediatric liquids [15, 21]. Descriptive sensory work on sweetened beverages also shows that consumer response depends on the combined sensory profile rather than sweetness alone, which supports multi-feature optimization rather than one-variable reformulation [28]. The resulting formulation guidance would be a rank-ordered set of rational changes, such as reducing bitterness exposure, adjusting sweetener blend, lowering mouth-coating viscosity, or selecting a more compatible taste-masking strategy [24].

Integration Into Pediatric Formulation Workflow

Early-Stage Screening of Taste-Masking Strategies

During pre-formulation, a predictive palatability model could be used to compare candidate taste-masking strategies before committing to expensive or ethically sensitive pediatric sensory work [13]. Cyclodextrin complexation, multiparticulate taste masking, and related excipient approaches can be represented as structured formulation features, allowing the model to estimate whether a strategy would be expected to improve acceptability for a given bitterness profile [7, 8]. Electronic-tongue data could then provide an early instrumental check that a proposed masking approach has reduced the measurable bitterness signal [20]. This workflow would not eliminate human panels, but it could prioritize the most defensible candidates for later acceptability evaluation [5].

Table 2 shows a structured comparison of candidate taste-masking strategies used in predictive palatability modelling during pre-formulation, linking formulation design features with expected sensory outcomes and instrumental verification methods.

Table 2. Predictive comparison of taste-masking strategies and associated formulation features in pre-formulation palatability modelling

Taste-masking strategy	Mechanism of action	Key formulation features (model inputs)	Expected effect on bitterness perception	Electronic-tongue (in vitro) signal outcome
Cyclodextrin complexation	Inclusion complex formation reduces free drug concentration in saliva	Drug–cyclodextrin binding affinity, complex stability constant, drug hydrophobicity	Reduced immediate bitterness due to lower free drug availability	Decreased bitterness intensity and delayed release signature
Multiparticulate coating (e.g., pellets, beads)	Physical barrier prevents drug dissolution in oral cavity	Coating thickness, polymer type, dissolution pH threshold, particle size distribution	Strong reduction in early taste exposure	Suppressed early bitterness spike, delayed signal onset
Ion-exchange resins	Drug binding via reversible ionic interactions	Resin capacity, drug ionization state (pKa), binding kinetics	Reduced bitterness until drug is released in GI conditions	Lower initial bitterness signal with gradual release pattern
Sweeteners/flavour modifiers	Taste receptor modulation and bitterness masking	Sweetener concentration, flavour profile, bitterness intensity ratio	Partial masking; improves palatability without eliminating bitterness	Moderate reduction in bitterness signal; altered sensory profile
Lipid-based formulations	Drug partitioning into lipid phase reduces oral exposure	Lipid solubility, emulsifier system, droplet size	Reduced perceived bitterness via decreased aqueous availability	Lower and smoother bitterness curve
Solid dispersion systems	Molecular-level dispersion reduces crystalline drug exposure variability	Polymer matrix type, drug loading, dispersion uniformity	Variable reduction depending on release kinetics	Moderately reduced bitterness with formulation-dependent variability

Supporting Age-Specific Formulation Design

Age-specific formulation design is important because infants, toddlers, school-age children, adolescents, caregivers, and adult proxies may differ in sensory perception, communication ability, and willingness to continue a medicine [4]. The model could therefore be stratified by age group or include age-related descriptors so that predictions are not forced into a single average pediatric response [2]. Acceptability instruments designed for pediatric oral medicines and clinical palatability studies can provide structured outcomes for this type of modeling when their context and respondent type are preserved [6, 14]. For liquid medicines, age-specific prediction should also consider swallowability and viscosity because textural tolerance may vary across developmental stages and clinical conditions [22].

Evaluation Strategy

Predictive Accuracy

Predictive accuracy should be evaluated using held-out formulations that differ from the training set by API or formulation family, because random splitting at the record level may exaggerate apparent generalization [11]. Continuous acceptability predictions could be assessed conceptually using regression error criteria, while acceptable-or-unacceptable decisions could be evaluated using classification criteria appropriate for formulation screening [3]. The evaluation should also examine whether predictions remain stable across different outcome instruments, such as hedonic ratings, caregiver reports, and observed refusal [1]. Because this is a conceptual predictive-modeling framework, evaluation metrics should be specified as planned endpoints rather than reported as achieved numerical performance [13].

Sensitivity to API Bitterness and Sweetener Range

Sensitivity analysis should test whether predictions behave plausibly when API bitterness is high, sweetener concentration is low, or viscosity moves toward extremes that could affect mouthfeel and swallowing [9]. Sweetener dose-response and temporal sweetness evidence can define reasonable boundaries for virtual formulation changes, reducing the risk that the model recommends implausible concentrations or ignores lingering side tastes [18, 19]. Electronic-tongue qualification concerns should be considered when extrapolating from sensor signals, because a large instrumental bitterness distance may not have the same acceptability meaning across all excipient matrices [10]. The model should therefore be evaluated for monotonicity, interaction behavior, and extrapolation risk rather than only for average predictive performance [12].

Prospective Experimental Validation

Prospective validation would require selecting model-guided formulation modifications and comparing predicted acceptability with future human or trained-panel assessment, while avoiding claims of success before such studies are conducted [27]. A staged design could begin with adult or trained sensory assessment, proceed through electronic-tongue confirmation, and then use pediatric or caregiver acceptability evaluation only for candidates that are ethically and clinically justified [4, 5]. Published examples of pediatric formulation acceptability studies demonstrate how prospective work can document palatability,

swallowing, and willingness-to-take outcomes under controlled conditions [14, 25]. Such validation would be essential before using the model to support high-stakes formulation decisions in pediatric development programs [6].

Table 3 presents an evaluation and implementation framework for determining whether the proposed palatability model is accurate, interpretable, generalizable, and suitable for responsible formulation decision support.

Table 3. Evaluation and Implementation Framework for Interpretable Pediatric Palatability Modeling

Evaluation or implementation dimension	Why it matters for pediatric liquid palatability	Recommended analytical approach	Failure mode addressed	Decision-use implication
Formulation-family generalization	Records from the same API or formulation platform may be near-duplicates, creating overly optimistic performance estimates	Use API-held-out, formulation-family-held-out, or grouped cross-validation rather than random record-level splitting	Model appears accurate because it memorizes related formulations	Determines whether predictions can guide new formulation candidates rather than only explain familiar ones
Outcome harmonization	Pediatric studies use heterogeneous rating systems, caregiver reports, observed refusal measures, and sensory scales	Map outcomes to a common acceptability construct while preserving original instrument metadata	Non-equivalent outcomes are treated as identical labels	Allows the model to support screening while respecting differences among acceptability instruments
Electronic-tongue calibration	Instrumental bitterness signals do not automatically represent child acceptability	Evaluate correlation with human bitterness scores and acceptability outcomes within product-relevant matrices	Sensor response is overinterpreted as a complete sensory substitute	Positions electronic-tongue data as a supportive surrogate rather than a replacement for human assessment
Interaction plausibility	Palatability depends on combined sweetness, bitterness, viscosity, aftertaste, and age-related tolerance	Conduct sensitivity analysis for bitterness × sweetness, bitterness × viscosity, sweetener × aftertaste, and age × texture interactions	Model gives technically accurate but sensorially implausible recommendations	Ensures virtual screening respects known sensory and formulation constraints
Uncertainty and out-of-domain detection	Novel APIs, unusual excipient systems, or rare viscosity ranges may lie outside the training experience	Report prediction intervals, confidence bands, similarity-to-training indicators, or out-of-domain warnings	Model provides overconfident guidance for unsupported formulation space	Helps decide when experimental testing is required before relying on model guidance
Interpretability for reformulation	Formulators need to know which modifiable variable drives poor predicted acceptability	Use feature-attribution summaries, local explanations, partial-dependence trends, and interaction explanations	Prediction is delivered as a black-box score without actionable reformulation insight	Converts model output into specific formulation actions such as masking, sweetener adjustment, or viscosity modification
Bias from unpublished failures	Failed or unacceptable prototypes may be underrepresented in published data	Track data provenance, include internal negative examples when available, and evaluate class imbalance	Model learns an unrealistically favorable formulation landscape	Improves rejection-risk detection and prevents overestimation of candidate acceptability
Prospective validation pathway	Conceptual performance must be tested before high-stakes formulation decisions	Stage validation from virtual screening to electronic-tongue confirmation, trained/adult panel testing, and ethically justified pediatric or caregiver assessment	The framework is adopted before real-world predictive value is established	Defines a responsible pathway from model-guided screening to confirmatory human evidence
Human oversight and ethical use	Pediatric acceptability decisions involve child welfare, caregiver burden, and clinical context	Require formulation-scientist review and ethical justification before pediatric testing or development decisions	Automated predictions replace expert and ethical judgment	Keeps the model positioned as decision support, not as an autonomous pediatric formulation authority

Limitations

E-Tongue–Human Correlation Limitations

Electronic tongues can detect formulation differences and bitterness-related sensor patterns, but they cannot fully represent aroma, trigeminal sensations, aftertaste, visual expectation, or the emotional context of giving medicine to a child [9]. Their usefulness depends on calibration against relevant human sensory data and on qualification for the specific product class, excipient matrix, and bitterness mechanism being studied [10]. Even when electronic-tongue signals improve after taste masking, human acceptability may remain limited by viscosity, residual aftertaste, color expectation, or swallowing discomfort [17, 21]. Therefore, the model's reliability would be bounded by the quality of the mapping between instrumental bitterness, sensory perception, and observed pediatric acceptance [2].

Limited Chemical Diversity in Training Data

A predictive palatability model may underperform for novel APIs, unfamiliar bitterness profiles, or excipient combinations that are not represented in the historical training data [11]. Pharmaceutical palatability datasets are especially vulnerable to limited diversity because unsuccessful prototypes may remain unpublished, and published studies often focus on specific products or narrow formulation classes [3]. The model may also struggle when taste masking depends on mechanisms not fully captured by composition features, such as microstructural coating behavior, drug release in saliva, or complexation strength [24]. For this reason, predictions should be accompanied by uncertainty information and used to prioritize experimental work rather than to replace formulation judgment [8].

Conclusion

A machine learning model for pediatric liquid palatability could integrate sweetener type and concentration, bitterness measurements, viscosity descriptors, and historical acceptability outcomes into a single formulation decision-support framework. Its main purpose would be to estimate acceptability and rejection risk before every candidate formulation is advanced to human evaluation. Such a model would be most useful when it treats palatability as a combined sensory and administration outcome rather than as sweetness or bitterness alone.

The strength of this approach is that it would convert scattered formulation and sensory observations into interpretable guidance for development teams. Instead of relying only on trial-and-error reformulation, scientists could use model outputs to identify whether bitterness masking, sweetener adjustment, viscosity modification, or sensory-expectation changes are the most rational next step. This could make early-stage screening faster and more consistent while preserving human acceptability studies for the most promising candidates.

Important challenges would remain. Electronic-tongue signals must be carefully linked to human perception, and pediatric acceptability outcomes must be standardized without erasing meaningful differences among age groups, respondents, and study contexts. The model would also need broad chemical and formulation diversity to avoid overconfidence when applied to unfamiliar APIs or excipient combinations.

Progress in this area will depend on collaborative efforts to build shared pediatric palatability datasets that combine objective measurements with well-described sensory and acceptability outcomes. A standardized resource spanning APIs, sweeteners, taste-masking systems, viscosities, and age groups would enable more reliable predictive modeling. With careful validation, predictive palatability tools could become a practical bridge between formulation science, sensory science, and child-centered medicine development.

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