From Predictive Accuracy to Patient Acceptability and Beyond: Evidence from AI-Optimized Formulation to Patient Outcomes

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Abstract
Artificial intelligence (AI) and machine learning are increasingly applied to pharmaceutical formulation development, enabling prediction of drug bitterness, tablet properties, dissolution behaviour, and three-dimensional (3D) printing performance. However, improved predictive accuracy does not necessarily translate into medicines that patients accept or take as intended. This review evaluates the extent to which current evidence connects AI-guided formulation optimization with patient acceptability, medication-taking behaviour, and clinical outcomes. A narrative review of peer-reviewed literature published between January 2020 and October 2026 was conducted using exploratory searches covering AI-based formulation development, taste masking, palatability, swallowability, adherence, and patient outcomes, particularly in paediatric and older populations. The evidence demonstrated that AI models can predict formulation-related and laboratory properties, including bitterness classification and 3D-printing performance. However, direct validation against human acceptability remains limited. Related non-AI studies indicate that dosage-form characteristics, palatability, swallowability, and age influence medicine acceptability and administration. Nevertheless, these findings cannot establish the benefits of AI-optimized formulations. Within the literature retrieved, no direct evidence was identified demonstrating improvements in medication-taking behaviour, adherence, persistence, or clinical outcomes attributable to AI-guided formulation optimization. These findings highlight a substantial gap between computational performance and demonstrated patient benefit. Future research should integrate standardized patient-centred datasets, external model validation, prospective human acceptability studies, and direct measurement of medication use and clinical outcomes. Ultimately, AI-guided formulation development should be evaluated not only by predictive accuracy but also by its demonstrated contribution to safe, acceptable, and effective medication use.

Keywords: Artificial intelligence, pharmaceutical formulation, Patient acceptability, Palatability, Medication adherence, Clinical outcomes.

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1. Introduction

Developing an oral medicine has traditionally relied on iterative, trial-and-error cycles in which excipients, processes, and dosage-form dimensions are adjusted until stability, release, and manufacturability targets are met (Wu et al., 2025). Assessment of a drug's aversive taste may occur relatively late in development. The aversive taste of a drug, for example, is often assessed only during clinical development, so a bitter candidate may require reformulation, with associated delays and costs (Margulis et al., 2020). Patient-centred design aims to bring palatability, swallowability, dose flexibility, and ease of administration into early development decisions instead of treating them as downstream corrections (Hauber et al., 2024).

These attributes are especially important in groups for whom standard products fit poorly. Bitterness is common among active ingredients, roughly one in four being predicted by a machine-learning classifier to be intensely bitter (Margulis et al., 2020), and children rated bitter-flavoured tablets as less acceptable than adults did (Hofmanová et al., 2020). Taste masking, including the use of bitter-blocking excipients, is one response (Andrews et al., 2020). Ethical and practical constraints often prevent taste

evaluation in the target paediatric population (Yoo et al., 2023). Electronic tongues, which are analytical taste-sensing instruments (Imam & Nagpal, 2023), can be used to select promising samples before a human sensory panel confirms taste masking (Guedes et al., 2020). EMA guidance expects the acceptability of tablet size and shape to be justified for the target age group (Agency, 2013), and reviews describe a shift toward small solid dosage forms for children (Khan et al., 2022). This shift raises questions of swallowability and dose accuracy across age groups (Lura et al., 2025).

Among older adults, swallowing disorders are common, with a pooled prevalence of about 56% across seven studies in residential aged care, although individual estimates ranged from 16% to 69.6% (Roberts et al., 2024). Large tablets may be poorly accepted by those with dysphagia (Vallet et al., 2020).

Artificial intelligence has entered this landscape as a way to reduce experimental burden and to navigate complex formulation spaces (Ros et al., 2026). Machine-learning models have been developed to classify the bitterness of molecules from their structure (Fritz et al., 2021), to predict the printability of three-dimensional (3D) printed medicines (Elbadawi et al., 2020), and to interpret children's facial reactions to taste strips (Aziza et al., 2024). Reviews discuss AI as a potential means of supporting personalised approaches, including analysis of real-world patient data (Vora et al., 2023). These proposed benefits should not be read as evidence that AI-guided formulation optimisation has already improved adherence or clinical outcomes. Concerns remain about data quality (Trinh et al., 2021), interpretability (Ros et al., 2026), regulatory acceptance, and ethics (Mirakhori & Niazi, 2025).

The examples above are predictive rather than optimising: each estimates a property of a molecule, a formulation, or a patient reaction, rather than selecting a formulation against patient-facing targets. The central gap addressed here is whether model-led optimisation translates into outcomes that matter to patients. A formulation can be optimal for a measurable laboratory target without being the most acceptable medicine for the person who must take it (Desai et al., 2020), and a model that predicts a laboratory property accurately has not thereby shown that people find the product acceptable, that they take it as intended, or that they benefit clinically. These are distinct endpoints, and evidence for one does not establish the next (Menditto et al., 2020).

This review examines how far current evidence extends from AI-guided pharmaceutical formulation optimisation to outcomes that matter to patients. Here, AI-guided formulation optimisation refers to the use of machine-learning models to select or refine formulation composition, process parameters, or dosage-form attributes against defined targets. It follows a proposed evidence chain of five stages: computational prediction (including AI-based formulation design and attribute prediction), laboratory assessment, human acceptability, medication-taking behaviour, and clinical outcomes. By distinguishing direct AI-linked evidence from adjacent non-AI evidence, the review identifies where the evidence is established, where it remains limited, and what is needed to demonstrate meaningful patient benefit. Section 2 describes how the literature was identified and grouped, and the sections that follow examine the evidence at each of these stages.

2. Scope and Approach of the Narrative Review

This review draws on peer-reviewed scientific literature published between January 2020 and October 2026. Searches were conducted in October 2026 through a web-based search interface returning journal, PubMed Central, and publisher records. Search concepts covered artificial intelligence and machine learning (e.g., Ros et al., 2026); pharmaceutical formulation, 3D printing, and mini-tablets (e.g., Münch, Kloft, et al., 2023; Münch, Sessler, et al., 2023); bitterness, taste masking, palatability, and electronic-tongue assessment (e.g., Steiner et al., 2024); swallowability (e.g., Vallet et al., 2020); acceptability, adherence, and clinical outcomes (e.g., Menditto et al., 2020); and paediatric and older populations (e.g., Hummler et al., 2023; Münch, Kloft, et al., 2023; Münch, Sessler, et al., 2023). The searches were exploratory rather than structured database-specific searches with reproducible search strings (Sukhera, 2022).

Only peer-reviewed publications in scientific journals were used as sources of evidence; websites, preprints, conference abstracts, dissertations, and other grey literature were excluded. Regulatory guidance (Agency, 2013) is cited for context only and was not treated as evidence of effect. Publications were selected for discussion if they illustrated a specific stage of the evidence chain, and each was read for the endpoint it actually measured. Where AI-specific studies did not extend to downstream endpoints, selected non-AI studies were included as clearly labelled adjacent evidence. Findings were grouped by stage rather than by study, so a single paper may appear under more than one heading.

The studies discussed map onto the five stages of the evidence chain: computational prediction (Fritz et al., 2021); laboratory assessment (for example, electronic-tongue or in vitro measurements) (Kojima et al., 2021); human acceptability (taste panels, questionnaires, observer-reported or self-reported measures) (Hofmanová et al., 2020); behavioural outcomes (observed administration, intake, or adherence; stated willingness is treated separately as a patient-proximal measure) (Vallet et al., 2020); and clinical outcomes (for example, biomarker control in treated patients, represented here by adjacent non-AI evidence linking an adherence-knowledge score to metabolic control in type 1

diabetes) (Dilek & Çömlek, 2025). These stages describe what was measured and do not rank study quality. Statements that no study was identified refer only to the material retrieved here.

3. AI Approaches Relevant to Patient-Centred Formulation Optimisation

Machine-learning models used in formulation work are mostly supervised: they learn a mapping from inputs, such as molecular descriptors, excipient composition, or process settings, to a measured property (Jiang et al., 2022). Classical algorithms, including random forests, boosted trees, and support vector machines, are common for small tabular datasets (Djuriš et al., 2021), whereas artificial neural networks can capture non-linear relationships among formulation variables (Abdelrahman & Klinken, 2025), and genetic algorithms have been coupled with them for inverse design (Ali et al., 2024). Model choice should depend on the question, dataset size, and need for interpretability rather than on an assumption that more complex algorithms are better (Makarov et al., 2021). For taste, models usually operate on chemical structure and classify compounds as bitter or not, or as very bitter or not (Kou et al., 2023), and graphical interfaces have been built to make them usable by formulators (Bai et al., 2021). For 3D printing, models have been trained on datasets of several hundred formulations to predict printability and related properties (Elbadawi et al., 2020).

Computer vision is relevant where product characteristics or human responses are observable. Machine-vision models have been trained to detect defects in tablets from surface images (Diószegi et al., 2024) and to automate in vitro testing of 3D-printed orodispersible films (O'Reilly et al., 2021), and facial landmarks extracted from videos of children tasting flavoured strips have been used to train models that classify taste and hedonic score (Aziza et al., 2024). Such approaches aim to provide a more objective record of reaction than verbal report alone, although facial reactions can be complex and variable (Aziza et al., 2024).

Natural language processing could in principle extract preferences, complaints, and patient feedback from free text. Within the material retrieved for this review, however, we did not identify peer-reviewed studies that used NLP to inform formulation design from patient feedback.

These methods are integrated with experimentation in several ways (Figure 1). Predictions can prioritise which compounds need taste masking before formulation work begins (Margulis et al., 2020); they can narrow the set of 3D-printing formulations worth making (Elbadawi et al., 2020); Bayesian optimisation and active learning can propose the next most informative experiment (Elbadawi et al., 2026); and human panel data can be fed back to retrain models, an approach advocated for palatable paediatric formulation development (Yoo et al., 2023). Model outputs must nevertheless be kept distinct from patient-centred outcomes: a model of dissolution time addresses formulation performance, a model of taste-sensor response addresses an instrumental proxy, and only a model trained on human ratings can address acceptability more directly (Yoo et al., 2023). Section 5 examines what these models predict and how they have been validated.

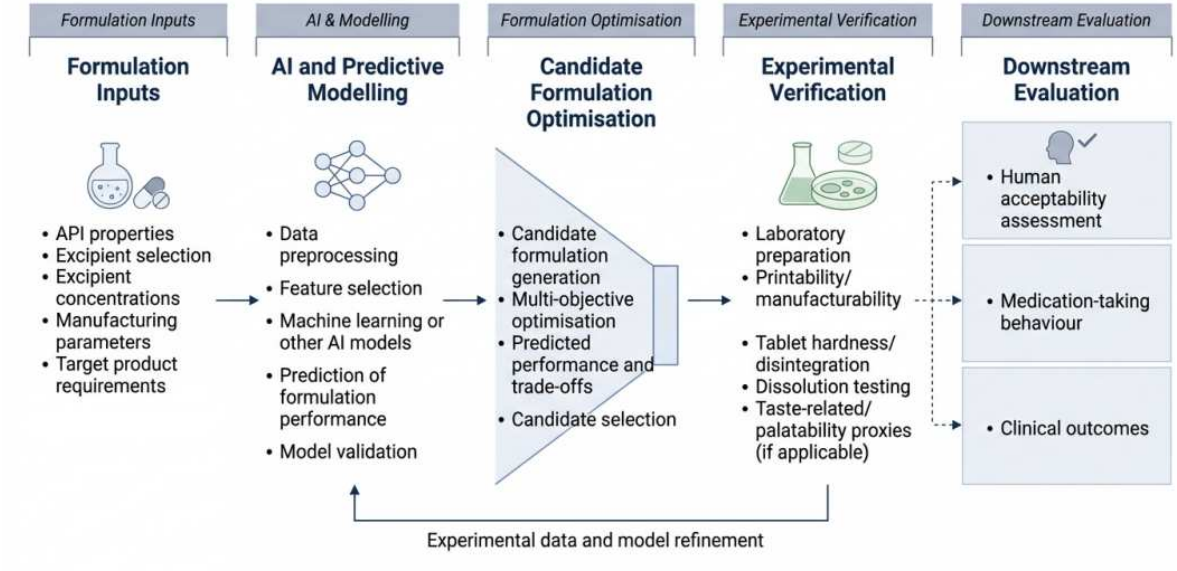


Figure 1. *Conceptual workflow of AI-guided pharmaceutical formulation optimisation and experimental validation. Formulation inputs inform predictive modelling and candidate selection, while experimental findings support verification and iterative model refinement. Human acceptability, medication-taking behaviour and clinical outcomes require separate downstream evaluation and cannot be inferred from computational predictions or laboratory*

performance alone.

4. Patient-Centred Attributes and Their Assessment

Acceptability is multidimensional and context dependent. It may include palatability, swallowability, mouthfeel, appearance, ease of administration, handling, and the effort required from patients or caregivers, and the relative importance of each differs by age, ability, disease, and setting (Reidemeister et al., 2023). Acceptability rests on distinct attributes such as palatability, swallowability and appearance, so assessment should report the specific attributes measured (Tuleu et al., 2020).

Taste and palatability are the most developed attributes in this literature. Bitterness is a major barrier for paediatric medicines (Andrews et al., 2020), and taste-masking performance has traditionally been judged by trained or screened human panels, in vitro methods, or surrogate assays (Guedes et al., 2020). Because testing in children is often impractical, it has been proposed that healthy young adults aged 18 to 40 years can serve as substitutes owing to similar taste sensitivity, provided panellists are screened for bitterness detection thresholds and a reference product is used (Yoo et al., 2023), although adults' palatability ratings cannot be assumed to translate directly to children (Hofmanová et al., 2020). Palatability also depends on excipients and on the dosage form, not only on the drug (Menditto et al., 2020).

Swallowability and dosage-form dimensions are central for both age extremes. In children aged 2 to under 7 years, a randomised study of 300 participants found that drug-free film-coated 3 mm mini-tablets reached acceptability rates of at least 80%, with swallowability of at least 42% and palatability of at least 82% across groups (Münch et al., 2023). A later randomised study using a composite acceptability endpoint found age-specific differences: mini-tablets had the highest acceptability in infants and children aged 6 to under 12 years, whereas oblong tablets were most acceptable in adolescents (Münch et al., 2024). In older adults, an observational study of 938 observer reports of tablet intake found that tablets under 6.5 mm appeared to be accepted by patients with swallowing disorders, whereas 83% of the 309 tablets assessed were 6.5 mm or larger (Vallet et al., 2020).

Dose flexibility and individualised administration matter where weight-based or titrated dosing is needed (Januskaite et al., 2020). Fixed-strength products can force splitting, crushing, or compounding, and such alterations are commonly applied, especially for children (Zahn et al., 2020). Mini-tablets and 3D printing are two routes to flexibility (Vaz & Kumar, 2021), the latter proposed as a means of on-demand production of customisable medicines (Krause et al., 2021). Personalisation must still preserve content uniformity, stability, and release characteristics (Melocchi et al., 2020). Appearance matters too: colour, shape, and markings may aid identification (Shariff et al., 2020), but similar-looking medicines can cause confusion in polypharmacy (Plácido et al., 2021).

Texture and other sensory attributes can also influence acceptability. In a feasibility study of 30 children aged 4 to 12 years, all of whom had previously taken part in a conventional-tablet swallowing study, placebo FDM-printed tablets were rated acceptable by 87% for mouthfeel or texture and by 93% for taste, and 77% said they would be happy to take such a tablet every day if it were a medicine (Bracken et al., 2022).

Non-AI assessment methods provide the reference points against which AI predictions are judged. They include human taste panels, electronic-tongue (e-tongue) measurements (Guedes et al., 2020), in vitro taste-related and dissolution assays, physical proxies such as wettability and mucoadhesion tests (Ershad et al., 2021), and swallowability or acceptability measures such as questionnaires, observer-reported outcomes (Vallet et al., 2020), magnetic resonance imaging of oesophageal transit (Hummler et al., 2024), and composite endpoints that combine palatability and swallowability (Reidemeister et al., 2023). The e-tongue is a liquid-phase method that measures dissolved compounds (Khalid et al., 2020), so for other dosage forms it is typically applied to drug released into a dissolution medium. In a study of four reconstituted amoxicillin–clavulanic acid suspensions followed over several days, e-tongue results tracked taste deterioration of the suspension over the dosing interval (Zaid et al., 2022). Such agreement is encouraging, but instrumental and laboratory measures are proxies and are not automatically equivalent to direct human acceptability, particularly in children (Guedes et al., 2020): an e-tongue cannot discriminate complex flavour mixtures (Khalid et al., 2020), and rapid in vitro disintegration does not capture infant chewing behaviour,(n.d.) and caregiver manipulation of tablets can change the dose a child receives (Binson et al., 2021). Table 1 summarises the attributes discussed and the main limitation of each assessment approach.

Table 1. Patient-centred attributes of pharmaceutical formulations and methods of assessment

Patient-centred attribute	What should be assessed	Assessment methods	Important limitation
Taste and palatability	Bitterness and taste perception; Taste perception (including bitterness); separately, willingness to take the	Human taste panels, electronic tongue (e-tongue), and in vitro taste-related assays (Guedes et al., 2020)	Instrumental measurements may not fully reflect human sensory experience (Guedes et al., 2020).

	medicine as a reported acceptability or intention outcome, and observed medication-taking behaviour as a downstream administration outcome		
Swallowability	Ability to swallow the dosage form	Swallowability questionnaires, observer-reported outcomes, and composite acceptability measures (Vallet et al., 2020)	Acceptability and swallowability are distinct outcomes (Münch et al., 2023).
Mouthfeel and texture	Oral texture and sensory experience during administration	Human sensory assessment and relevant physical or sensory tests (Hofmanová et al., 2021)	Laboratory proxies cannot fully reproduce the experience of taking a medicine (Hofmanová et al., 2021).
Appearance and identification	Colour, shape, markings, and ease of identifying the medicine	Visual assessment and patient or caregiver feedback (Plácido et al., 2021)	Similar-looking medicines may cause confusion, particularly in polypharmacy (Plácido et al., 2021).
Ease of administration and handling	Practical difficulties during preparation and administration	Questionnaires, observer reports, and assessment of administration procedures (Jani et al., 2021)	Findings may depend on age, ability, dosage form, and caregiver technique (Alessandrini et al., 2021).
Dose flexibility and individualisation	Suitability of dose adjustment and administration for individual needs	Assessment of dose requirements, dosage-form properties, and relevant formulation tests (Couți et al., 2025)	Personalisation must preserve content uniformity, stability, and release characteristics (Couți et al., 2025).
Overall acceptability	Combined experience of taking a medicine	Questionnaires, composite endpoints, and patient or caregiver assessments (Reidemeister et al., 2023)	A global score may obscure an unacceptable individual attribute; therefore, component scores should be reported alongside it where feasible (Hauber et al., 2024).

Note. Citations identify representative sources discussed in Section 4; they support the listed assessment methods or limitations and do not imply that every method has been validated for every attribute.

5. From Predictive Accuracy to Patient Acceptability and Outcomes

The proposed evidence chain has five stages: computational prediction (including AI-guided formulation design and attribute prediction), laboratory assessment, human acceptability, medication-taking behaviour, and clinical outcomes. Each stage must be examined on its own endpoint, because success at an upstream computational stage does not guarantee downstream clinical utility.

5.1. What AI Predicts and How Prediction Is Evaluated

The targets that AI models predict fall into two groups. The first comprises molecular, formulation, and process variables and laboratory properties. Bitterness classifiers predict whether a compound is bitter or very bitter from structure (Margulis et al., 2020), while M3DISEEN predicts the printability of medicines from a dataset of 614 drug-loaded formulations built from 145 excipients (Elbadawi et al., 2020). These are inputs and laboratory properties, not patient-centred endpoints. The second group is closer to the patient: facial-reaction models were trained to classify the taste of strips and children's hedonic scores (Aziza et al., 2024), and it has been argued that panel acceptability scores should be used as training targets, which remains largely a proposal (Yoo et al., 2023).

Where performance is reported, it is almost always technical. The BitterIntense classifier achieved above 80% accuracy on several test sets, and about 25% of drugs were predicted to be very bitter (Margulis et al., 2020). VirtualTaste, which predicts sweet, bitter, and sour endpoints, reported overall accuracy of 90% and an area under the curve of 0.98 in 10-fold cross-validation and in an independent test set (Fritz et al., 2021). These figures show that structure-based prediction of a taste class is feasible, but validation practice varies and the reported metrics describe agreement with curated labels, not with the experience of a child taking a particular formulation (Malavolta et al., 2022).

Bitterness models have been trained on compounds collected from published literature and open databases (Bai et al., 2021). Most models are evaluated by cross-validation or held-out test sets on retrospective datasets that are often generated in a single laboratory or compiled from the literature, so evaluation stops at the laboratory bench: formulation datasets are often small, and retrospective cross-validation can indicate performance only if the model is never used to guide decisions (Kearnes, 2020). Consequently, external validity cannot be assumed, and prospective evaluation in independent cohorts, using human sensory endpoints rather than curated labels alone, is needed before such predictions can inform formulation decisions for paediatric medicines (Desai et al., 2020).

5.2. Validation Against Human Acceptability

Direct validation against human responses is scarce for AI-informed work. In one study, 197 videos and 256 self-reported hedonic scores were collected from 64 children, and the expected hedonic pattern emerged, with sweetness liked and bitterness disliked (Aziza et al., 2024). The authors highlighted the complexity and variability of facial reactions and identified eyebrow and mouth-corner elevations as indicators of palatability (Aziza et al., 2024). This is a direct comparison with human responses, but the stimuli were flavoured taste strips rather than finished formulations, so the link from a predicted formulation attribute to acceptability of an actual product was not tested (Aziza et al., 2024).

The closest bridge between an instrumental model and human experience among the papers identified is a study of binder-jetting 3D-printed levetiracetam instant-dissolving tablets designed for paediatric and dysphagic patients. An e-tongue with principal component analysis and factorial response-surface modelling was used to optimise taste-masking additives, a sweetener and spearmint flavour (Wang et al., 2021), and a human taste panel of 10 healthy adults (mean age 26.7 ± 2.3 years) using a visual analogue scale then yielded numerically higher VAS scores than the non-taste-masked formulation, with the human results consistent with the trend of the electronic tongue evaluation (Wang et al., 2021). The target, however, was an instrumental taste-sensing system and not a general AI model of patient acceptability, and the panel comprised healthy adults. The study supports the narrower conclusion that e-tongue data can assist taste-masking decisions when confirmed by sensory evaluation (Wang et al., 2021).

Other validations are indirect. Structure-based bitterness models have been evaluated against curated compound labels and historical taste databases, which tests agreement with laboratory or database measures and not with human acceptability (Margulis et al., 2020). A critical view on the qualification of electronic tongues found reliable protocols for qualified instrumental performance, proper taste-masking assessment, and, under certain circumstances, the evaluation of bitterness, but also cautioned that measured samples must be in solution, that sensors respond differently to charged and uncharged molecules, and that interactions between formulation components can lead to misleading results (Steiner et al., 2024). A review of taste-panel use also recommended incorporating human panel data into model training because surrogate methods have limitations (Yoo et al., 2023).

Comparisons between human outcomes and laboratory proxies exist mainly outside AI, with a systematic review finding that around a third of taste-evaluation studies used an e-tongue and a human sensory panel together and recommending that the sensory panel be applied to confirm the taste masking suggested by the instrument (Guedes et al., 2020). For swallowing, a non-AI study found that the favourable in vitro slip of film-coated tablets correlated with the in vivo sensory ratings of slipperiness and stickiness given by a human panel (Hofmanová et al., 2021), and MRI measurements in healthy volunteers compared oesophageal transit of solid dosage forms with different surface materials (Hummler et al., 2024). This is adjacent evidence, not evidence for AI, and it concerns healthy-volunteer ratings rather than children's acceptability of AI-optimised products. No AI-guided study retrieved here validated predicted tablet attributes against human swallowing endpoints.

Thus, the evidence base we retrieved supports a distinction that should be kept explicit. Validation against laboratory measurements is common, whereas direct validation against human acceptability of AI-optimised formulations was not identified. Where human data exist, they are small, use simplified stimuli, or come from non-AI work.

5.3. From Acceptability to Medication-Taking Behaviour

We found no peer-reviewed study that linked AI-informed formulation work to willingness to take medicines, administration experience, or adherence. This was the finding of the searches reported here and should not be read as proof that no such study exists. A scoping review of 3D-printed personalised paediatric medicines examined real-world evidence on their potential in children with cancer (Ahmed et al., 2024); a parallel review of paediatric 3D printing noted that although there is substantial technical and in vitro data, its translation into clinical practice is still limited and only a few studies have targeted clinical efficacy (Couți et al., 2025).

Willingness, adherence, and persistence are different outcomes. Acceptability describes the overall ability and willingness of the patient to use, and of any caregiver to administer, the medicine as intended at the point of administration (Hofmanová et al., 2020). Adherence is the extent to which actual medicine-taking corresponds to the agreed

regimen, and persistence is the length of time from initiation to discontinuation of therapy (Menditto et al., 2020); persistence requires longitudinal measurement and cannot be inferred from a single acceptability rating, since patients who regularly skip doses may be non-adherent yet persistent (Ferrín et al., 2024). None of the studies discussed below measured persistence, and none is treated as doing so.

Selected non-AI studies illustrate what behaviour-proximal evidence looks like and are labelled as adjacent evidence that cannot establish an AI effect. In older adults, observer-completed questionnaires filled in real time during medication rounds have been used to capture how a medicine is actually administered (Jani et al., 2021), and of 938 observer reports, tablets were classified as accepted in older patients without dysphagia (n = 790) but not in those with swallowing disorders (n = 146). These subgroup counts total 936; the reason for the two-report discrepancy is unclear from the reported figures (Vallet et al., 2020). In a randomised crossover study of 40 children in two age groups, 80% of infants aged 6–11 months (95% CI: 56–94%) swallowed the mini-tablets without chewing, compared with 22% and 35% who swallowed dispersed fine granules and liquid formulations without leftover, whereas no significant differences were seen in toddlers aged 12–23 months (Mitsui et al., 2022). By contrast, children who said they would be happy to take a 3D-printed tablet daily expressed a willingness and not an observed adherence, with 77% reporting they would be happy to take the tablet every day if it were a medicine (Bracken et al., 2022).

Computational tools have also been used to analyse adherence rather than to formulate the medicine: natural language processing of free-text responses from patients with type 2 diabetes identified regimen complexity and disruption of daily routines as barriers to adherence (Chan et al., 2024), and a qualitative study identified the treatment attributes that shape perceived complexity (Stewart et al., 2023), but no AI-optimised dosage form was involved.

These studies are informative for endpoint selection: observer-reported acceptability has been assessed in older adults (Jani et al., 2021). However, single-administration studies with placebo or drug-free products, such as single-dose studies of drug-free, film-coated mini-tablets (Münch, Kloft, et al., 2023; Münch, Sessler, et al., 2023), do not establish continued use, and none involved a formulation designed or selected by an AI model. Direct tests would need to record missed or refused doses, dose completion, caregiver burden, and reasons for discontinuation, using prospectively collected measures and clinically appropriate comparators. Acceptability may mediate this pathway, but it is not a substitute for measuring the behaviour itself.

5.4. From Formulation Performance to Patient or Clinical Outcomes

Patient or clinical outcomes may include successful administration of the intended dose, fewer administration errors, improved symptom control, reduced treatment failure, better quality of life, or lower healthcare utilisation, depending on the medicine and population. We did not identify AI-informed formulation studies that directly measured such outcomes. The AI-linked literature retrieved here stops at computational prediction, laboratory properties, or limited human sensory responses, and studies of 3D printing adoption in pharmacy practice report long lags between proven effectiveness and routine clinical use (Algahtani, 2021). Under the search limits described in Section 2, the absence of direct studies is itself a finding.

Non-AI studies show what clinical-outcome evidence can look like, and their results should not be attributed to AI optimisation. In a paediatric clinical study, 3D-printed chewable medicines containing amino acids (citrulline, isoleucine, valine, and combinations) were prepared in a hospital setting and compared with conventional compounded medicines in six children with rare metabolic disorders (Rodríguez-Pombo et al., 2024). Amino acid levels were controlled within target ranges as well as with conventional medicines, and the deviation of citrulline levels was narrower and closer to the target concentration with the chewable formulations (Rodríguez-Pombo et al., 2024). This study measured a patient-relevant biomarker outcome, but its sample was very small and the printing was not reported as being guided by a machine-learning model.

Where AI has been linked to clinical care in the retrieved literature, the intervention was clinical decision support rather than dosage-form design, for example in dose optimisation and adverse-drug-event prediction (Alowais et al., 2023); prescribing decision support systems have been examined for their effects on physician practice performance and patient outcomes across a wide range of diseases including cardiovascular disease, hypertension, diabetes and kidney disease (Moghadam et al., 2021). Other non-AI evidence shows why the downstream stages matter: in type 2 diabetes, higher adherence is associated with improved glycaemic control (Scarton et al., 2023), and low medication adherence has been linked to poor glycaemic control in type 2 diabetes populations (Lubaki et al., 2022), and in children and adolescents with type 1 diabetes, an adherence-knowledge score has been linked to metabolic control (Dilek & Çömlek, 2025). In paediatric infection, adherence is of the utmost importance to prevent the emergence of resistant bacteria, and acceptability is likely to have a significant impact on compliance (Vallet et al., 2021). The hospital study of antibiotics measured behavioural acceptability, including negative reactions, restraint use and use of extra devices in observed intakes, rather than microbiological cure (Klingmann et al., 2023). A patient-preferred

product may still fail to improve health if dose delivery, efficacy, or safety is inadequate.

5.5. Evidence-to-Outcome Synthesis Framework

Figure 2 presents a proposed conceptual framework, not an established or validated model. It orders the evidence into five stages, to be read as a sequence of testable propositions rather than an automatic progression: computational prediction; laboratory assessment; human acceptability; medication-taking behaviour; and clinical outcomes. Table 2 summarises the status of each stage after examining the retrieved literature.

Three points follow. First, evidence is strongest for the earliest stages, where computational and laboratory prediction is well developed (Elbadawi et al., 2020). Second, support thins quickly after that: human validation is limited and mostly uses simplified stimuli (Guedes et al., 2020), and evidence at the behaviour and outcome stages was not found for AI-informed formulations. Third, evidence for one stage does not establish the next. A well-performing bitterness classifier (Margulis et al., 2020) does not show that a taste-masked product is acceptable (Wang et al., 2021), acceptability in a single-dose study does not show persistence (Ferrín et al., 2024), and biomarker control in non-AI work does not show that AI optimisation improves clinical outcomes (Rodríguez-Pombo et al., 2024).

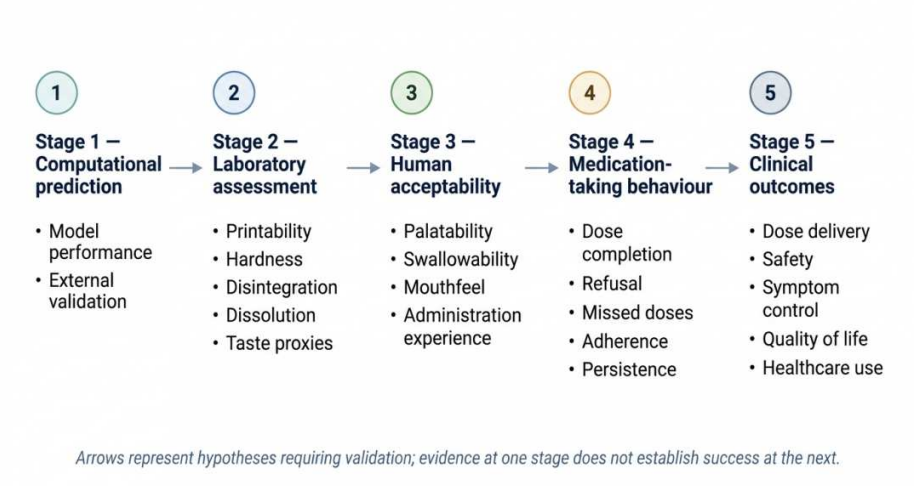


Figure 2. *Proposed five-stage evidence-to-outcome framework. The framework illustrates the proposed progression from computational prediction and laboratory assessment to human acceptability, medication-taking behaviour, and clinical outcomes. Each stage represents a distinct domain of evaluation, from model performance and formulation properties to patient experience, medication use, and health outcomes. Arrows represent hypotheses requiring validation; evidence at one stage does not establish success at the next.*

Table 2. Evidence status across the proposed five-stage framework

Evidence stage	Status in retrieved literature	Interpretation / next validation need
1. Computational prediction	Relatively strongest; technical metrics reported for selected models (Elbadawi et al., 2020).	Report independent/external validation and robustness across datasets.
2. Laboratory assessment	Common; includes formulation properties and instrumental taste proxies (Elbadawi et al., 2020; Guedes et al., 2020; Momeni et al., 2024).	Validate across formulations, equipment, process settings and laboratories.
3. Human acceptability	Limited; adjacent human-acceptability evidence—not direct validation of AI-optimised formulations—including facial-response work on taste strips and small sensory panels. No study identified directly validates an AI-optimised formulation. (Aziza et al., 2024; Wang et al., 2021).	Test finished formulations with relevant patient groups and validated measures.
4. Medication-taking behaviour	No AI-informed formulation study identified in this review that measured behaviour directly; adjacent evidence informs acceptability measurement (Wargenau et al., 2022).	Measure dose completion/refusal, missed doses, caregiver burden and adherence prospectively.
5. Clinical outcomes	No AI-informed formulation study identified in this review that directly measured clinical outcomes; available clinical examples are non-AI (Couți et al., 2025).	Use suitable comparators and assess safety, dose delivery, disease control and patient-relevant outcomes.

6. Barriers to Translation and Future Directions

6.1. Data and Measurement

Datasets are the first constraint (Elbadawi et al., 2026). Taste-prediction models are built on chemically diverse compounds, while the aversive taste of drugs is typically tested only late in clinical trials (Margulis et al., 2020), and

the cited data-driven flavor-chemistry work does not establish that drug taste-prediction models are limited to particular compound classes (Kou et al., 2023). Formulation datasets of roughly 600 to nearly 1,000 entries exist for physical parameters such as printability, tablet hardness, and disintegration time (Muñiz et al., 2021), but datasets that pair quantitative excipient compositions with standardised human acceptability outcomes are largely absent in the literature retrieved, partly because sensory testing in children is rarely seen (Guedes et al., 2020). Outcome definitions are also inconsistent: acceptability has been operationalised through different approaches, including composite-endpoint development and patient- and caregiver-reported questionnaires (Reidemeister et al., 2023; Turner-Bowker et al., 2020); this review distinguishes acceptability, palatability, willingness, adherence, and persistence as separate outcomes and does not assume that authors use these terms interchangeably, which complicates pooling data for model training.

6.2. Model Validation and Generalisability

Models trained on small or curated datasets risk overfitting and may not transfer to new compounds, formulations, or populations (Stokes et al., 2020). Reporting of data splitting, leakage, uncertainty, and testing across dosage forms remains uneven in the literature retrieved, although general machine-learning guidance calls for it (Artrith et al., 2021). Transferability to children is a specific concern: variability in facial reactions has been reported, and facial-expression models developed on adults may not capture differences in children (Cheong et al., 2021). A model that generalises across laboratory dissolution media also does not automatically generalise across human variability in pH, motility, and transit times (Vinarov et al., 2021). Validation should therefore be repeated in the target population and with finished formulations, and prospective evaluation, with uncertainty reported, would show whether performance holds outside the data on which models were developed (Artrith et al., 2021).

6.3. Equity, Ethics, and Patient Representation

Acceptability differs across age, ability, and preference (Alessandrini et al., 2021). The preferred dosage form changes from infancy to adolescence (Alessandrini et al., 2021), swallowing disorders change which tablet sizes are accepted (Vallet et al., 2020), and regional traditions shape formulation familiarity. A model trained mainly on healthy adults or adult panels may embed their preferences (Norori et al., 2021), and the use of young adults as taste-panel substitutes for children is a pragmatic choice that has limits (Yoo et al., 2023). Interpretability and ethical considerations, including bias and transparency, are repeatedly raised in reviews of AI in drug development and health systems (Lopes et al., 2026). Representation should be considered at the design stage, with early engagement of patients and caregivers (Alessandrini et al., 2021), and patient choice should not be reduced to a single model-derived acceptability score (Turner-Bowker et al., 2020).

6.4. Regulation and Translation into Practice

Regulatory acceptance of AI-derived evidence remains an open issue (Mirakhori & Niazi, 2025). AI-guided development must coexist with established requirements for quality, safety, efficacy, and manufacturing control, and a model cannot replace testing of content uniformity, stability, dissolution, or dose accuracy (Melocchi et al., 2020). Study design should be proportionate to the claim: a taste-masking claim needs human sensory validation (Yoo et al., 2023), an adherence claim needs longitudinal medication-use measures (Ferrín et al., 2024), and a clinical-benefit claim needs an appropriate clinical endpoint (Sande et al., 2024). A composite acceptability endpoint with validation evidence (Wargenau et al., 2022), alongside clearly defined observer-reported outcome frameworks,could serve as common measures (Reidemeister et al., 2023), and developers and regulators would benefit from clarity on what evidence of patient benefit is expected when AI selects or optimises a formulation, since laboratory validation alone does not answer that question (Mirakhori & Niazi, 2025). A hospital-based paediatric clinical study of 3D-printed personalised medicines shows that patient-relevant outcomes can be collected in practice (Rodríguez-Pombo et al., 2024).

Priorities follow from the gaps identified. Standardised patient-centred datasets that pair formulation descriptors with human acceptability measures would allow models to be trained and tested against the endpoints that matter (Yoo et al., 2023). Collaboration between formulation scientists, clinical pharmacists, and clinicians is needed to define relevant populations, measures, and settings (Walsh et al., 2021), so that models optimise clinically meaningful attributes rather than isolated laboratory parameters (Sande et al., 2024). Finally, validation must move beyond laboratory performance to human acceptability, behaviour, and clinical outcomes, with persistence measured explicitly where it is the question (Ferrín et al., 2024).

7. Conclusion

The evidence reviewed supports the first two stages of the chain: AI models can predict computational and laboratory properties relevant to patient-centred formulation, such as bitterness class and 3D-printing performance (Bai et al., 2021; Muñiz et al., 2021). Support for the third stage, human acceptability, is limited: direct comparisons with human responses are few, small, and based on simplified stimuli, while most validation is against laboratory or database measures (Aziza et al., 2024). The stages of medication-taking behaviour and clinical outcomes were not demonstrated for AI-informed formulations in the literature retrieved (Ahmed et al., 2024). Where such evidence exists, it comes from non-AI studies of 3D-printed medicines (Rodríguez-Pombo et al., 2024).

The evidence is therefore strongest for computational and laboratory prediction, weaker for human acceptability validation, and absent, within this search, for behavioural and clinical endpoints. Prediction accuracy alone does not demonstrate acceptability, adherence, persistence, or clinical benefit, and these endpoints should be treated as distinct (Ferrín et al., 2024).

To move AI-guided formulation toward demonstrably patient-centred practice, the field needs prospective studies that test AI-optimised formulations against validated human acceptability endpoints in the intended paediatric and geriatric populations (Turner-Bowker et al., 2020), followed by studies measuring medication-taking behaviour and persistence (Ferrín et al., 2024), and where feasible, patient or clinical outcomes (Sande et al., 2024). Standardised datasets, external validation, and transparent reporting will be needed so that gains in predictive accuracy can be linked to gains for patients (Artrith et al., 2021). AI-guided formulation development will become genuinely patient-centred only when models are judged not just by how accurately they predict product properties, but by whether the resulting medicines work safely and acceptably for the people who need to take them (AI-guided formulation development will become genuinely patient-centred only when models are judged not just by how accurately they predict product properties, but by whether the resulting medicines work safely and acceptably for the people who need to take them.

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