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Beyond Solubility Enhancement: Multiobjective Formulation Design for Bioavailability, Stability, Manufacturability, Safety, and Patient Acceptability across Development Stages

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ABSTRACT

Pharmaceutical formulation development is frequently organized around a dominant technical obstacle, with poor aqueous solubility often treated as the principal variable to be corrected. Although solubility enhancement may improve dissolution or create favorable exposure hypotheses, it does not by itself establish dosage-form viability, because the resulting formulation may remain unstable, difficult to manufacture, unsafe for the intended population, or unacceptable in actual use. This article develops an original, non-empirical Multiobjective Formulation Design Framework that treats biopharmaceutical performance, physical, chemical, and microbiological stability, manufacturability and control, excipient and product safety, and patient acceptability as coupled design domains. The framework separates optimizable objectives from non-compensatory constraints and organizes formulation decisions through candidate and process variables, an objective vector, a hard-constraint gate, explicit characterization of evidence and uncertainty, an evidence-adjusted feasible design space, a stage-conditioned Pareto set, and a traceable governance record. Excipient safety and patient acceptability are positioned as design-defining considerations rather than downstream checks. Trade-off analysis is used to identify defensible compromise candidates without implying that any formulation is universally optimal. Stage-specific evidence requirements determine which claims may be supported during discovery, preformulation, process development, clinical translation, and lifecycle management. The original contribution is the integration of previously separated formulation domains into a reversible decision architecture in which candidate status depends on evidence relevance, uncertainty, development stage, and context of use. Computational predictions, laboratory measurements, manufacturing studies, stability-indicating methods, population-specific acceptability assessments, and clinically relevant performance evidence remain necessary for validation. The framework does not establish product-specific superiority, clinical benefit, regulatory acceptability, or deployment readiness.

Key words: *Formulation, Pharmaceutical formulation, Dosage form, Excipient, Manufacturability, Stability*
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INTRODUCTION

Pharmaceutical formulation extends beyond improving an isolated physicochemical property. It requires designing a drug product whose material attributes, dosage form, administration conditions, and patient interactions collectively support safe, effective, and practical use. Patient-centric design therefore treats formulation as a benefit–risk and usability problem shaped by the intended population and use environment [1].

Dosage-form attributes such as size, shape, dose flexibility, frequency, sensory properties, packaging, device requirements, and manipulation can affect real-world use and should be considered within the target product profile [2]. Although these attributes do not independently guarantee adherence or clinical benefit, ignoring them can produce technically advanced formulations that are poorly suited to patients or caregivers.

Patient-centric development should therefore translate patient, clinical, manufacturing, and stakeholder needs into measurable product objectives [3]. This article proposes a non-empirical multiobjective framework integrating biopharmaceutical performance, stability, manufacturability, safety, and acceptability. It distinguishes mechanistic rationale, prediction, experimental confirmation, clinical relevance, and decision readiness. Rather than providing a universal algorithm, it offers a structured approach for identifying feasible candidates, comparing trade-offs, documenting uncertainty, and revising decisions as evidence develops.

Why single-objective solubility optimization fails

Solubility enhancement may improve dissolution and potential drug availability, but measured gains can represent equilibrium solubility, transient supersaturation, colloid-associated drug, or molecularly dissolved drug, each with different implications for absorption. Enabling systems such as amorphous solid dispersions may improve dissolution while introducing precipitation, stability, processing, and control risks [4-6]. Their value therefore depends on whether the enhanced state survives manufacturing, storage, administration, gastrointestinal transfer, and the required absorption period.

Manufacturing methods can produce similar apparent solubility gains while differing substantially in thermal or solvent exposure, residual-solvent risk, particle properties, scale-up requirements, and downstream processability [5]. Biopharmaceutical performance is likewise influenced by precipitation kinetics, dose, permeability, gastrointestinal conditions, and the persistence of molecularly available drug [6]. A large but brief apparent concentration may therefore be less useful than a smaller, sustained dissolved concentration.

Definition of formulation objectives and constraints

A formulation objective is a desired, measurable product outcome for which alternative levels may be compared, whereas a constraint defines whether a candidate is permissible within a stated development context. Decision variables are the controllable or selectable features used to generate candidates, including API form, excipient identity and concentration, dosage-form architecture, release mechanism, process route, operating conditions, packaging, and assumptions about administration. Quality-by-design approaches establish that critical material attributes and critical process parameters must be related to critical quality attributes, but these categories are linked rather than interchangeable [7]. An input such as polymer grade is not itself an objective, a processing temperature is not a product outcome, and a critical quality attribute does not automatically specify the preference or feasibility rule used to compare formulations.

The proposed objective vector contains five domains: biopharmaceutical performance; physical, chemical, and microbiological stability; manufacturability and control; excipient and product safety; and patient acceptability. Each domain may contain multiple product-specific measures, and evidence may be computational, experimental, manufacturing-derived, clinically informed, or population-specific. Compatibility predictions can help prioritize drug–excipient combinations and identify potentially unfavorable interactions, but predictive output remains screening evidence rather than proof of compatibility [8]. Experimental confirmation is still required because model transferability depends on the represented chemical space, formulation conditions, measurements, data quality, and endpoint definition. Prediction, verification, validation, and decision use must therefore remain separate stages.

Evidence quality and uncertainty are treated as separate state variables rather than hidden within objective scores. Two candidates with similar predicted performance should not necessarily receive the same decision status when one is supported by relevant replicated measurements and the other depends on extrapolation from sparse or incompatible data. The evidence state records provenance, relevance, uncertainty, validation level, and transferability for each objective estimate. This separation prevents confidence from being mistaken for performance and allows a candidate to be classified as promising but insufficiently supported. The classification of a factor as an objective or constraint must remain product-specific and revisable: manufacturability may be an optimizable burden at one stage but become a hard feasibility limit when reproducible production cannot be demonstrated.

Proposed multiobjective design framework

Data-driven formulation methods can expand the searchable design space by linking composition, processing, and product attributes to predicted outputs or by generating candidate structures that would be difficult to enumerate manually. Their value nevertheless depends on the definition of meaningful target outputs, the provenance and representativeness of training data, the interpretation of uncertainty, and experimental validation. Machine-learning and generative approaches may accelerate candidate exploration, but they do not eliminate the need to establish pharmaceutical feasibility or decision relevance [9-11]. **Figure 1** presents the original conceptual synthesis for multiobjective formulation-design space, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

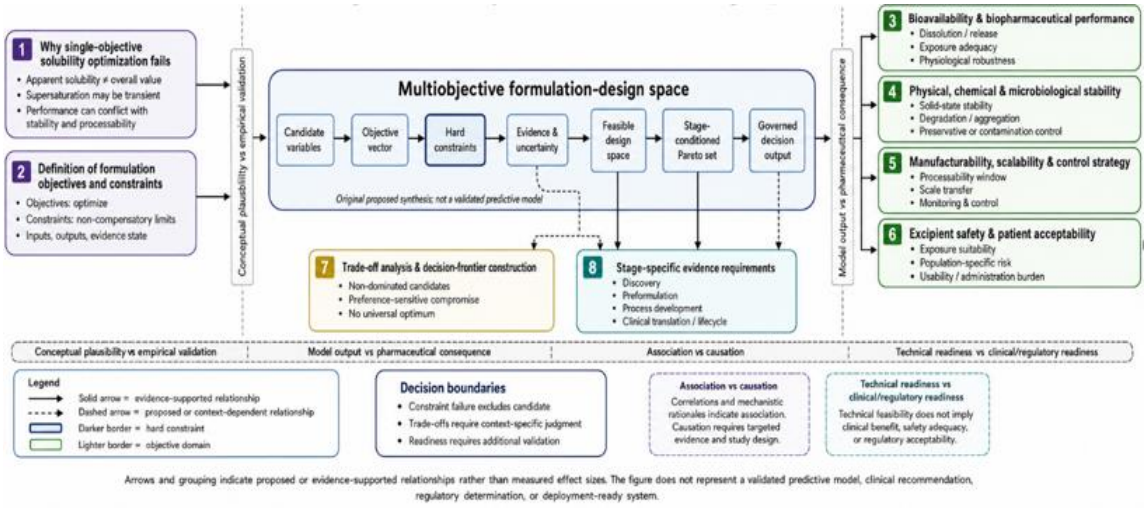

Figure 1. Multiobjective Formulation-Design Space.

The framework begins with a candidate-generation layer containing formulation and process variables. Candidate generation may be experimental, mechanistic, data-driven, expert-directed, or hybrid, but generated candidates are treated as hypotheses rather than accepted solutions. A generative method can propose particle or formulation structures and may support experimental exploration, yet its outputs still require evaluation against material behavior, product specifications, manufacturing conditions, and intended use [11].

Bioavailability and biopharmaceutical performance

Bioavailability is treated in the proposed framework as a multidimensional performance domain rather than a direct consequence of solubility. Physiologically based biopharmaceutics modelling can connect formulation attributes, dissolution behavior, gastrointestinal processes, and systemic exposure hypotheses, thereby extending evaluation beyond isolated in vitro measurements [12]. Such models are especially useful when they clarify which formulation variables are expected to influence absorption. Their outputs nevertheless remain conditional on model structure, parameter quality, verification, sensitivity analysis, and the relevance of the simulated physiological conditions.

Long-acting formulations further demonstrate why performance cannot be reduced to peak dissolution or apparent concentration. Their intended value depends on reproducible release, preservation of molecular integrity, administration feasibility, tolerability, dose loading, and maintenance of the desired exposure profile. Technologies developed for fragile molecules illustrate how formulation composition, depot formation, degradation, delivery route, and manufacturing requirements interact when prolonged release is pursued [13]. Adaptive or long-acting release should therefore be defined as a controlled temporal-performance objective, not as proof that a formulation will improve clinical outcomes.

For supersaturating oral systems, the concentration that is mechanistically available for membrane transport may be more informative than total apparent drug concentration. Distinguishing molecularly dissolved drug from colloidal, precipitated, or otherwise associated material can improve the interpretation of absorption models and formulation comparisons [14]. This distinction does not establish that one analytical method is universally sufficient. Measurement relevance depends on compound properties, medium composition, gastrointestinal transfer conditions, sampling design, and the mechanism by which the formulation maintains or loses supersaturation.

The framework consequently defines biopharmaceutical performance as a proposed vector comprising exposure adequacy, exposure variability, robustness to relevant physiological conditions, release fidelity, and the persistence of absorbable drug. These elements should be selected according to the dosage form and intended context of use. Dissolution enhancement, model-predicted exposure, or prolonged release may justify further development, but none alone establishes therapeutic efficacy, bioequivalence, clinical benefit, or suitability for a particular patient population.

Table 1 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for definitions, components, relationships, and intended uses in beyond solubility enhancement..

Table 1. Definitions, components, relationships, and intended uses in Beyond Solubility Enhancement.

Component or scientific dimension	Problem addressed	Inputs or determinants	Proposed mechanism or relationship	Expected contribution	Evidence required	Failure or uncertainty risk	Boundary statement
Solubility and supersaturation	Insufficient molecular availability may restrict dissolution and absorption.	API form, ionization, medium, excipients, dose, precipitation inhibitors.	**Evidence-supported:** supersaturation may increase available concentration but remains vulnerable to precipitation [6]. **Proposed:** it is one input to, rather than a surrogate for, total formulation value.	Supports selection of enabling strategies without allowing solubility to dominate unrelated objectives.	Equilibrium and kinetic solubility, precipitation behavior, transfer testing, and relevant concentration measurements.	Apparent concentration may be mistaken for molecularly available drug.	Solubility improvement does not establish bioavailability, stability, or product readiness.
Biopharmaceutical performance	Dissolution results may not translate directly into systemic exposure.	Dissolution, permeability, gastrointestinal conditions, dose, release kinetics, physiological variability.	**Evidence-supported:** mechanistic models may connect formulation inputs with exposure hypotheses [12]. **Proposed:** performance is represented as a vector rather than a single endpoint.	Organizes exposure adequacy, variability, robustness, and release fidelity.	Mechanistic model qualification, discriminatory in vitro testing, in vivo relevance, and sensitivity analysis.	Model misspecification or non-representative physiological assumptions may create false confidence.	Predicted exposure does not demonstrate clinical efficacy or bioequivalence.
Mechanistically relevant concentration	Bulk concentration may include non-absorbable or transiently associated drug.	Molecularly dissolved fraction, colloids, precipitate, sampling method, medium composition.	**Evidence-supported:** molecularly dissolved concentration can improve absorption prediction for supersaturatin	Improves interpretation of dissolution and absorption relationships.	Validated separation or analytical method and context-specific model comparison.	Analytical processing may alter the measured species or miss rapid transitions.	One concentration metric is not universally adequate for every dosage form.

			g formulations [14].				
Long-acting or adaptive release	Extended duration may be pursued without adequate release reproducibility or molecular protection.	Depot architecture, carrier degradation, drug loading, administration route, molecular fragility.	**Evidence-supported:** long-acting performance depends on release, stability, administration, and technological feasibility [13].	Broadens performance evaluation from duration alone to release fidelity and administration feasibility.	In vitro release, stability-indicating analysis, administration testing, pharmacokinetic relevance, and process reproducibility.	Burst release, incomplete release, degradation, or administration burden may offset duration.	Prolonged release does not establish improved adherence, safety, or clinical benefit.
Stability domain	Initial performance may deteriorate during manufacture, storage, transport, or use.	Composition, moisture, temperature, interfaces, process stress, container, microbial exposure.	**Proposed original framework category:** physical, chemical, and microbiological stability are evaluated as distinct but interacting sub-objectives.	Prevents favorable early performance from concealing later product deterioration.	Product-specific degradation, phase behavior, microbiological-control, package, and in-use evidence.	Incompatible test conditions or short observation periods may conceal relevant failure modes.	No universal shelf life, preservative level, or storage condition is implied.
Manufacturability and scalability	A laboratory formulation may not remain reproducible during dosage-form conversion or scale transfer.	Material attributes, process route, operating window, equipment, residence history, control capability.	**Evidence-supported:** formulation performance and processability can define a bounded operating window [15].	Integrates process feasibility with pharmaceutical performance before candidate selection.	Process mapping, material-flow characterization, scale-relevant trials, and control evidence.	Scale-dependent phase, flow, mixing, or thermal changes may invalidate bench findings.	Feasibility in one process or scale does not establish commercial manufacturability.
Excipient safety	Functional excipients may create exposure or compatibility concerns.	Identity, grade, concentration, route, duration, population vulnerability, impurities.	**Proposed:** unacceptable product-specific exposure is treated as a non-compensatory constraint.	Prevents performance gains from numerically offsetting severe safety concerns.	Toxicological, exposure, compatibility, route-, duration-, and population-specific assessment.	Historical use may be applied outside its relevant dose, route, or population.	The framework does not classify any excipient as universally safe or unsafe.
Patient acceptability	Technically effective dosage forms may remain difficult to administer or use.	Size, shape, sensory attributes, dose frequency, device, manipulation, packaging, population needs.	**Evidence-supported:** dosage-form attributes may influence medication-taking behavior [2]. **Proposed:** acceptability enters stage-specific candidate comparison.	Connects product design with intended users and administration conditions.	Population-relevant usability, sensory, administration, and access evidence.	Proxy judgments by developers may not represent intended patients or caregivers.	Acceptability evidence does not by itself demonstrate adherence or therapeutic benefit.

Hard constraints and feasible design space	Preference scoring can conceal essential product failures.	Essential-quality requirements, safety limits, stability, dose accuracy, administration feasibility.	**Proposed:** candidates must satisfy declared non-compensatory constraints before trade-off analysis.	Defines which candidates may legitimately enter comparative optimization.	Justified product-specific criteria and evidence sufficient for the development stage.	Incorrectly classified constraints may exclude useful candidates or admit unacceptable ones.	The framework supplies no universal numerical threshold or regulator-approved specification.
Evidence-adjusted decision use	Similar predicted values may be supported by substantially different evidence.	Provenance, relevance, uncertainty, validation level, transferability, development stage.	**Proposed:** candidate status is conditioned on both objective estimates and the evidence supporting them.	Makes uncertainty and evidence gaps visible in selection decisions.	Traceable data, uncertainty analysis, experimental confirmation, and context-of-use justification.	Sparse or transferred evidence may create unstable rankings.	Conceptual plausibility is not equivalent to empirical validation or decision readiness.

Physical, chemical, and microbiological stability

Physical stability concerns whether the formulation retains its intended material state, microstructure, distribution, and performance-relevant properties over time. In amorphous dispersions, polymer selection, drug loading, water uptake, and storage conditions can alter crystallization risk and phase behavior even when initial dissolution is favorable [16]. This evidence is formulation-specific and should not be generalized to every delivery platform. It nevertheless demonstrates that an enabling state must remain sufficiently stable throughout the relevant manufacturing and storage interval.

Chemical and conformational stability require a different analytical logic because deterioration may involve covalent degradation, oxidation, hydrolysis, deamidation, aggregation, unfolding, adsorption, or interfacial damage. Protein-formulation development illustrates how pH, buffer, excipients, process stress, container interactions, and storage conditions may influence distinct degradation pathways [17]. Mechanism-specific methods are therefore preferable to a single undifferentiated stability score. Evidence from protein products cannot be transferred automatically to small molecules, but it supports the broader requirement to align formulation controls with the actual degradation mechanism.

Microbiological stability becomes particularly important for aqueous, multidose, or repeatedly accessed products. Antimicrobial preservation must be evaluated together with API stability, excipient compatibility, package interactions, particle formation, route of administration, and the expected in-use period [18]. Preservative effectiveness alone is therefore insufficient if the preservative destabilizes the drug product or if formulation components reduce antimicrobial activity. Conversely, preservative-free strategies require evidence that the container, manufacturing process, handling controls, and use pattern adequately limit contamination risk.

The proposed framework represents physical, chemical, and microbiological stability as separate sub-objectives with distinct mechanisms, tests, and uncertainty sources. A stability concern may be treated as optimizable when it can be controlled within a justified operating region, but an unacceptable degradation, contamination, or essential-quality failure becomes a hard constraint. Superior bioavailability cannot compensate for such failure. These categories organize decision-making but do not establish product-specific shelf life, preservative concentration, storage condition, or release specification.

Manufacturability, scalability, and control strategy

Manufacturability is defined as the capacity to produce the intended dosage form reproducibly within justified material, equipment, process, and control conditions. Continuous manufacturing demonstrates that product quality depends on integrated process understanding rather than independent optimization of isolated unit operations [19]. Material transformations and disturbances can propagate across feeding, blending, granulation, drying, compression, coating, or other connected stages. Continuous processing is therefore neither presumed superior nor required by the proposed framework; its relevance depends on the product and manufacturing context.

Process analytical technology and advanced control can support real-time knowledge of material flow, residence-time behavior, critical attributes, and disturbance propagation. In continuous oral-solid manufacture, these

capabilities are linked with equipment integration, traceability, diversion strategies, raw-material variability, and the performance of the complete process train [20]. Monitoring does not remove these challenges. A technically capable sensor can still provide limited decision value when sampling is unrepresentative, the measured attribute is an unsuitable proxy, or the relationship to final product quality is insufficiently established.

Model predictive control extends process monitoring by using a dynamic model and measurements to estimate process state and select control actions. Its credible use requires qualified dynamics, observable variables, disturbance scenarios, actuator authority, constraint handling, and control logic that users can interpret and operate [21]. A model that performs under nominal simulations may fail when material properties drift or when unmodelled disturbances occur. Control validation must therefore address both technical performance and the conditions under which human intervention, alarm handling, or process diversion remains necessary.

Within the framework, manufacturability can function as either a soft objective or a hard feasibility gate. Processing time, yield burden, control complexity, or equipment demand may be compared as optimizable attributes when acceptable product quality remains achievable. In contrast, inability to produce a reproducible dosage form, maintain essential quality, or control a critical disturbance constitutes infeasibility at the relevant stage. This classification is product- and stage-dependent and does not recommend a particular manufacturing platform, scale-up pathway, or control algorithm.

Table 2 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for testable propositions, evidence requirements, and validation criteria for beyond solubility enhancement..

Table 2. Testable propositions, evidence requirements, and validation criteria for Beyond Solubility Enhancement.

Architecture layer or process stage	Core function	Information or material flow	Interaction with other components	Validation criterion	Potential failure mode	Human or experimental responsibility	Readiness boundary
Candidate-generation layer	Generate formulation and process hypotheses from mechanistic, experimental, expert, or computational inputs.	Candidate compositions, material forms, dosage-form structures, and operating conditions move to objective evaluation.	Depends on declared targets and available design variables.	Generated candidates can be reproduced and evaluated against predeclared pharmaceutical attributes.	Search outputs reflect biased data, unrealistic constraints, or non-manufacturable combinations.	Formulation scientists define the design domain and verify candidate plausibility; generated structures remain hypotheses [9].	Candidate generation alone does not establish feasibility or superiority.
Digital or generative exploration	Prioritize combinations that may be difficult to enumerate manually.	Data and target outputs are transformed into predictions or proposed structures.	Requires compatibility, stability, process, and use-context evaluation.	Prospective experiments test whether predicted relationships transfer to the intended domain.	Data-set shift, hidden confounding, poor uncertainty characterization, or optimization of an unsuitable proxy.	Data scientists document provenance and limitations; experimental teams independently test outputs [11].	Model output is not a pharmaceutical consequence or release decision.
Objective-definition layer	Translate product intent into measurable performance, stability, manufacturing, safety, and acceptability dimensions.	Target-product needs are converted into endpoint definitions and evidence plans.	Determines what candidate-generation and validation activities optimize.	Endpoints are measurable, discriminating, product-relevant, and linked to decision use.	Ambiguous or redundant objectives allow proxy performance to replace product value.	Cross-functional experts justify definitions and resolve incompatible measurement scales [7].	Objective definitions are proposed and product-specific, not universal criticality assignments.
Compatibility and	Detect potentially	Composition descriptors and	Feeds the stability and	Predictions are confirmed	A compatible prediction	Experimental confirmation	Predictive compatibility

uncertainty layer	unfavorable drug–excipient relationships and identify evidence limitations.	predicted interactions inform experimental prioritization.	safety domains and may restrict candidate generation.	using relevant physical, chemical, and process-stress studies.	conceals degradation, adsorption, reaction, or phase behavior.	remains mandatory because screening models do not replace compatibility testing [8].	does not establish long-term stability or safety.
Hard-constraint gate	Exclude candidates with unacceptable essential-quality, safety, stability, or administration failures.	Objective evidence is converted into a feasible or currently infeasible classification.	Operates before preference weighting or Pareto comparison.	Each exclusion criterion is product-specific, justified, traceable, and supported at the relevant stage.	A severe failure is diluted within an aggregate score or an uncertain result is treated as definitive.	Decision owners define escalation rules and request confirmatory evidence when classification is uncertain.	Passing the gate permits comparison; it does not establish clinical or regulatory readiness.
Evidence-adjusted feasible space	Combine candidate performance with provenance, relevance, uncertainty, and transferability.	Objective estimates and their evidence states define candidate eligibility.	Determines which candidates may enter trade-off analysis.	Candidate status remains stable under reasonable analytical and modelling alternatives or is explicitly labelled provisional.	Apparent feasibility depends on a fragile assumption, incompatible measurement, or unverified extrapolation.	Analysts perform sensitivity testing; subject-matter experts judge pharmaceutical relevance.	No universal confidence score or readiness threshold is supplied.
Process-integration and scale-transfer layer	Test whether formulation behavior survives connected processing and increasing scale.	Materials move through unit operations while attributes and disturbances propagate downstream.	Links formulation selection with equipment, residence history, monitoring, and final product quality.	Scale-relevant trials reproduce critical attributes within justified process conditions [19].	Flow, thermal history, mixing, or phase behavior changes during scale transfer.	Process scientists design representative trials and distinguish equipment effects from formulation effects.	Bench manufacturability does not establish commercial-scale capability.
Process monitoring and control layer	Observe relevant process states and manage disturbances.	Sensor data and material-flow information inform alarms, diversion, or control action.	Depends on process dynamics, attribute relevance, and actuator capability.	Measurements are representative and control actions maintain stated product-quality objectives [20].	Sensors monitor an unsuitable proxy or disturbances exceed model and actuator capability.	Engineers qualify sensors, models, alarms, diversion logic, and operator procedures [21].	Advanced control does not remove human oversight or validation obligations.
Development-stage gate	Match evidence depth to the consequence of the next decision.	Mechanistic, bench, pilot, clinical, and lifecycle evidence progressively constrain candidate status.	Revises feasible-space membership and objective priorities as development advances.	Evidence is relevant to the intended stage, population, process, and context of use.	Early evidence is used to support a later-stage claim without adequate transfer validation.	Governance teams declare the permitted decision use and unresolved evidence gaps.	Stage progression does not imply approval, therapeutic benefit, or deployment readiness.
Traceable governance record	Preserve the rationale for selecting, retaining,	Objectives, evidence, uncertainty, compromise	Connects every framework layer with	A decision can be reconstructed and revised	Preferences, assumptions, or exceptions remain implicit	Named scientific and decision owners	Documentation improves traceability but does not validate

	restricting, or rejecting a candidate.	rationale, responsibilities, and reversal triggers are recorded.	change control and later reassessment.	when specified new evidence emerges [3].	and become difficult to challenge.	maintain the record and authorize re-evaluation.	the underlying formulation.

Excipient safety and patient acceptability

Excipient safety must be assessed in relation to population, dose, route, duration, impurities, and evidence quality rather than inferred from compendial status or historical use [22]. Patient acceptability similarly depends on whether the dosage form can be used safely and correctly under realistic conditions, considering swallowing, dose flexibility, sensory properties, administration burden, packaging, and caregiver needs [23]. Safety and acceptability remain distinct, and serious safety or usability failures cannot be offset by advantages in bioavailability, convenience, or manufacturability.

Trade-off analysis and decision-frontier construction

When objectives conflict, formulation candidates should be compared as non-dominated compromise solutions rather than ranked against a universal optimum [24, 25]. Hard constraints, including unsafe exposure, unacceptable degradation, essential-quality failure, or unusable administration, must be applied before preference-based ranking. Among feasible candidates, priorities and uncertainty should be transparent, and frontier status should be classified as supported, provisional, or indeterminate. Final selection remains a governed judgment that records the chosen trade-off, evidence gaps, applied constraints, and conditions that could reverse the decision [3].

Stage-specific evidence requirements

Evidence requirements should increase with decision consequence. Models must be qualified for their intended use, inputs, assumptions, sensitivity, and relationship to meaningful product attributes [26]. Risk-based classification can guide which uncertainties must be resolved before progression [27]. Evidence should advance from mechanistic plausibility and bench verification to scale reproducibility, clinical relevance, patient acceptability, and lifecycle control. Although priorities may shift from learning during early development to reproducibility and control later, essential safety and quality constraints remain non-compensatory throughout [22, 23].

Limitations and implementation priorities

Algorithmic formulation development remains limited by heterogeneous data, incomplete metadata, inconsistent endpoint definitions, sparse negative results, and limited prospective evaluation. Recommendations for machine-learning applications emphasize transparent data provenance, appropriate validation, interpretable reporting, uncertainty assessment, and experimental confirmation [28]. These practices improve credibility but are not themselves validated standards. A technically sophisticated algorithm cannot compensate for a poorly defined objective, unrepresentative training domain, or absent product-specific confirmation.

The proposed feasible region may also be distorted when a formulation or manufacturing process is represented as static despite changing material states, disturbances, and temporal dependencies. Static characterization can be insufficient when process dynamics determine whether critical attributes remain controlled [29]. This limitation does not mean that conventional characterization is always inadequate; rather, dynamic methods become necessary when the decision depends on trajectories, residence histories, delayed responses, or disturbance propagation.

Figure 2 presents the original conceptual synthesis for pareto frontier across performance, manufacturability, safety, and acceptability, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

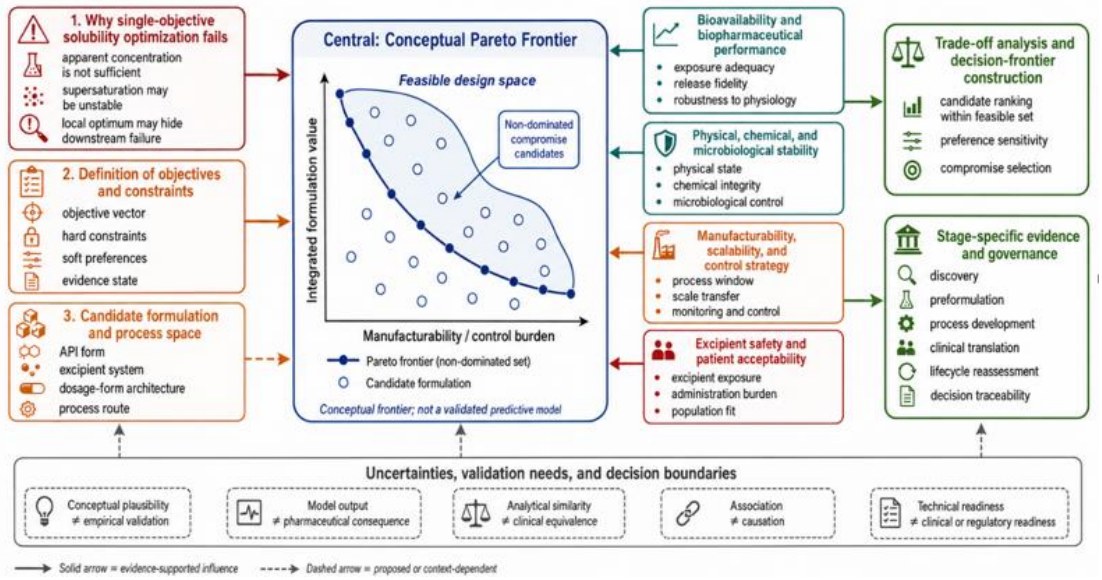

Figure 2. Pareto Frontier across Performance, Manufacturability, Safety, and Acceptability

Validation should test whether framework-guided decisions outperform single-objective choices on predeclared, product-specific outcomes without increasing violations of hard constraints. Multiobjective experiments can evaluate whether candidate diversity and compromise quality improve under uncertainty-aware search [24]. Context-of-use qualification should determine whether computational evidence supports the intended decision [26]. Prospective evaluation should also examine data transferability, experimental reproducibility, decision reversibility, and the practical burden of governance [28]. These are research priorities rather than claims that the framework improves product, clinical, manufacturing, safety, or regulatory outcomes.

CONCLUSION

This article proposes a Multiobjective Formulation Design Framework in which solubility enhancement is retained as an important technical strategy but is no longer treated as a sufficient indicator of formulation success. The framework integrates biopharmaceutical performance, stability, manufacturability and control, excipient and product safety, and patient acceptability through explicit objectives, non-compensatory constraints, evidence and uncertainty characterization, a stage-conditioned feasible design space, Pareto reasoning, and traceable governance. Its principal contribution is organizational and theoretical: it defines how heterogeneous evidence and competing objectives may be connected without converting predictions into pharmaceutical consequences or compromise solutions into universal rankings. The framework requires product-specific computational, experimental, manufacturing, clinical, acceptability, and lifecycle validation. It does not establish formulation superiority, clinical benefit, regulatory acceptance, universal applicability, or deployment readiness.

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