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FROM FORMULATION SEARCH TO THERAPEUTIC EXPOSURE: THE CHANGING ROLE OF ARTIFICIAL INTELLIGENCE IN ADVANCED DRUG-DELIVERY DEVELOPMENT

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ABSTRACT

Artificial intelligence is increasingly used to organize formulation variables, predict compatibility and release behavior, prioritize experimental candidates, and connect pharmaceutical data across development stages. Yet much of the current literature remains concentrated on narrowly bounded prediction tasks, whereas drug-delivery development ultimately requires evidence that a formulation can be manufactured reproducibly, generate the intended material behavior, control transport through biological environments, and produce therapeutically relevant exposure. This state-of-the-art review evaluates the changing role of artificial intelligence across that translation arc. The review applies an explicit evidence-selection and critical-appraisal logic to distinguish retrospective benchmark performance, experimentally confirmed capability, mechanistically linked prediction, prospective development utility, and routine pharmaceutical readiness. The resulting synthesis proposes that formulation artificial intelligence should not be treated as a single technological category. Instead, it comprises different evidence classes, including composition screening, compatibility assessment, release modeling, biodistribution prediction, biopharmaceutic and pharmacokinetic integration, manufacturing analytics, and closed-loop experimentation. The central contribution is an evidence-gated interpretation in which predictive models become pharmaceutically consequential only when their outputs remain valid across successive transitions from formulation search to material behavior, release, transport, exposure, and a bounded development decision. Current evidence is strongest for domain-specific prioritization and selected experimentally anchored workflows, whereas generalization across formulations, laboratories, manufacturing scales, biological contexts, and delivery modalities remains limited. The proposed synthesis is conceptual rather than empirically validated and does not constitute a regulatory or clinical framework. Its practical implication is that future pharmaceutical artificial intelligence should be evaluated by the quality of the decisions it supports, the uncertainty it exposes, and the evidence connecting its intermediate predictions to therapeutic exposure.

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Introduction

Artificial intelligence has expanded from isolated prediction of pharmaceutical properties toward broader support for formulation design, composition optimization, process selection, and experimental prioritization. Contemporary formulation-oriented applications include supervised prediction, optimization algorithms, representation learning, and emerging integration with automated experimentation. Lipid-nanoparticle development illustrates this widening scope because composition, processing, physical structure, and biological performance may all be treated as linked modeling targets. Nevertheless, the available evidence remains heterogeneous, and many models are trained on small, platform-specific datasets that represent

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only a restricted part of the feasible pharmaceutical design space [1–3]. The central scientific issue is therefore no longer whether an algorithm can detect formulation-associated patterns, but whether those patterns remain informative as development moves from a computationally ranked candidate to a manufactured product that produces reproducible exposure. This distinction matters because pharmaceutical development is a sequence of dependent decisions rather than a collection of independent prediction tasks. A model that predicts solubility, compatibility, encapsulation, particle formation, or release may improve one decision while remaining silent about downstream transport, biodistribution, target-site exposure, safety, or clinical usefulness. Broader analyses of machine learning across drug discovery and development similarly show that technical performance must be interpreted in relation to stage-specific data, experimental integration, and the decision context in which a model is intended to operate [4]. In advanced drug delivery, this dependency is especially consequential because formulation composition, processing history, material structure, biological environment, route of administration, and patient physiology jointly influence performance.

The unresolved conceptual gap is the absence of a sufficiently discriminating account of how artificial intelligence changes role across these linked stages. Formulation-search models commonly treat the task as a mapping from ingredients and process variables to an intermediate outcome. Release models add temporal behavior, whereas biodistribution and biopharmaceutic models introduce physiological structure. Manufacturing models shift the analytical target again, from candidate ranking to monitoring, control, transfer, and lifecycle consistency. These activities cannot be placed on a single maturity continuum solely by comparing model metrics because they differ in data-generating process, validation setting, causal proximity to therapeutic performance, and consequences of error. A high-performing compatibility classifier and a qualified exposure model may both be described as pharmaceutical artificial intelligence, yet they support fundamentally different claims.

This review therefore examines the technological frontier through an evidence-gated formulation-to-exposure perspective. Its objective is to determine what has been demonstrated in formulation screening and composition optimization, how material behavior, release, transport, and biodistribution are represented, and what additional evidence is required before these predictions can inform therapeutic-exposure or development decisions. The review proposes an original interpretive distinction among benchmark capability, plausible pharmaceutical utility, experimental confirmation, mechanistic or biopharmaceutic linkage, translational value, and routine readiness. These categories are not presented as validated maturity scores. They are used to prevent intermediate predictive success from being misrepresented as evidence of manufacturability, mechanism, clinical utility, regulatory acceptability, or deployment readiness.

Review Scope and State-of-the-Art Selection Approach

The review was designed as a state-of-the-art synthesis rather than a publication-by-publication catalogue or a quantitative meta-analysis. Its frontier was fixed at the most recent peer-reviewed evidence available for the intended manuscript year, with selection directed by the article's formulation-to-exposure argument. Methodological guidance for state-of-the-art reviews supports an explicit statement of purpose, selection logic, interpretive procedure, and intended knowledge contribution; transparent evidence-synthesis reporting further requires clear identification of search, eligibility, and synthesis decisions; and domain-based appraisal discourages reliance on a single undifferentiated quality score [5–7]. These principles were applied proportionately because the included evidence encompasses methodological reviews, retrospective predictive studies, mechanistic models, experimentally anchored investigations, manufacturing applications, and prospective automated workflows rather than one uniform study design.

Eligibility was determined by whether an article supported a precise claim about formulation search, material behavior, release, transport, biodistribution, therapeutic-exposure linkage, experimental validation, manufacturing, modality readiness, or translational evaluation. Evidence was coded according to the pharmaceutical task, data and application context, modeled output, validation setting, decision relevance, and principal risk of overstatement. Greater interpretive weight was assigned to evidence that linked model outputs to independent experiments, mechanistic structures, prospective decisions, or operational pharmaceutical settings. Retrospective performance was not rejected, but it was classified as evidence of within-domain predictive capability unless stronger validation was reported. Articles were also appraised for narrow sampling, ambiguous labels, restricted formulation diversity, dependence on one laboratory or platform, insufficient out-of-domain testing, and unsupported movement from association to mechanism or from prediction to therapeutic value.

The synthesis used five related evidence questions. First, what pharmaceutical object was represented: a molecule, excipient pair, composition, process, material structure, release profile, tissue-distribution pattern, or exposure trajectory? Second, what decision was the model intended to support? Third, how closely was the predicted endpoint connected to therapeutic performance? Fourth, what form of validation separated model fitting from pharmaceutical confirmation? Fifth, which uncertainty or contextual constraint limited transfer to a new formulation, delivery route, manufacturing setting, or patient population? This structure allowed convergent findings to be distinguished from superficially similar but evidentially different claims. **Table 1** organizes the evidence, constructs, and interpretation boundaries needed to develop review scope and state-of-the-art selection approach within the article's central argument.

Table 1. Evidence domains, core questions, scientific requirements, and interpretation boundaries for Review scope and state-of-the-art selection approach

Evidence Domain	Eligible Evidence or Method	Reported Capability or Claim	Strength of Support	Reproducibility or Bias Concern	Unresolved Gap
Review-Frontier Definition	State-of-the-art reviews, methodological guidance, transparent reporting frameworks, and domain-based appraisal approaches	The technological frontier can be organized by current architectures, validation practices, and readiness boundaries rather than publication chronology	Strong methodological support for transparent review logic; indirect support for the article-specific synthesis	Review categories may reflect author interpretation, and heterogeneous study designs resist simple comparison	Independent application of the proposed evidence categories to other pharmaceutical domains
Formulation-Search Evidence	Retrospective supervised learning, representation learning, compatibility classification, candidate ranking, and optimization studies	Models may prioritize formulations or identify relationships between composition and intermediate performance	Moderate support within represented datasets and formulation platforms	Small datasets, selective reporting, inconsistent labels, and restricted chemical or excipient diversity	External validation on new compounds, excipients, laboratories, and formulation platforms
Material-Behavior and Release Evidence	Dynamic release prediction, kinetic modeling, degradation or diffusion models, and experimentally anchored material studies	Formulation and structural variables may predict in vitro release behavior	Moderate support for platform-specific prediction	Assay dependence, limited material diversity, and weak connection between in vitro release and in vivo performance	Prospective linkage among material structure, release, absorption, and exposure
Transport and Biodistribution Evidence	Preclinical biodistribution datasets, machine-learning models, physiological simulation, and hybrid mechanistic architectures	Nanoparticle and experimental descriptors may contain predictive information about tissue distribution	Moderate preclinical support; limited human relevance	Species dependence, route heterogeneity, study-level confounding, and incomplete biological representation	Cross-species and human-relevant validation with explicit uncertainty
Therapeutic-Exposure Linkage	Physiologically based biopharmaceutics or pharmacokinetic modeling, in vitro–in vivo linkage, and product-development case studies	Formulation and dissolution information may support bounded exposure predictions	Stronger when the context of use and model qualification are explicit	Parameter uncertainty, model identifiability, physiological variability, and case-specific assumptions	Generalizable integration of data-driven formulation models with qualified exposure models
Experimental and Manufacturing Validation	Prospective formulation experiments, process analytical technology, continuous-manufacturing data, digital microstructure studies, and automated laboratories	Artificial intelligence may support experiment selection, quality estimation, monitoring, or closed-loop optimization	Variable; strongest for prospectively tested but narrowly bounded tasks	Equipment dependence, calibration transfer, scale effects, process drift, and laboratory-specific workflows	Multi-site, multi-scale, lifecycle validation against established development practice
Translational Readiness	Cross-modality reviews, industrial perspectives, patient-centered assessments, and critical pharmaceutical-AI analyses	Readiness depends on evidence beyond benchmark prediction, including manufacturing, use context, safety, and decision impact	Strong conceptual agreement; limited routine deployment evidence	Readiness terminology is inconsistently defined and may obscure modality-specific limitations	Common evidence-gated criteria that remain sensitive to route, platform, endpoint, and intended decision

AI In Formulation Screening and Composition Optimization

Formulation screening is the domain in which artificial intelligence most directly alters the traditional relationship between experimental search and pharmaceutical prior knowledge. The computational task is generally framed as learning a mapping from drug, excipient, composition, processing, or molecular descriptors to an intermediate formulation outcome. Deep-learning studies have shown that formulation-level data can contain sufficient structure to predict defined in vitro outcomes within the represented formulation domain [8]. This capability may reduce the number of combinations requiring initial laboratory evaluation, but its interpretation depends on how the outcome was labeled, whether the formulation space was adequately sampled, and whether the test set represents interpolation or a genuinely new pharmaceutical condition. The relevant claim is therefore bounded: a model may learn useful formulation–performance relationships without demonstrating that the resulting candidate is manufacturable, stable, safe, or therapeutically effective.

Nanocrystal feasibility prediction illustrates the value and limitation of this search-oriented role. Machine learning can organize drug-property patterns associated with previously successful or unsuccessful nanocrystal formulations and thereby assist candidate prioritization [9]. Such models may be scientifically useful when the alternative is an undirected search across many compounds and process conditions. However, the predicted category is derived from historical formulation decisions and experimental definitions, which may vary between laboratories or fail to capture important process variables. Classification of a drug as a promising nanocrystal candidate is therefore a hypothesis about formulation feasibility. It does not establish that an experimentally produced nanocrystal will possess the required size distribution, physical stability, dissolution behavior, scale-up characteristics, or in vivo performance.

A more structurally integrated form of formulation artificial intelligence appears in polymeric long-acting injectable development. Here, model inputs may include drug properties, polymer characteristics, composition variables, and formulation

conditions, whereas the output may concern release-related behavior or the prioritization of polymer–drug combinations. Platform-specific models have demonstrated that these relationships can be learned well enough to accelerate exploration within a defined long-acting formulation space [10]. The significance of this evidence is greater than simple molecular-property prediction because the model addresses a multicomponent delivery system and a temporally relevant outcome. Even so, its applicability remains conditional on the polymers, drugs, manufacturing procedures, and release assays represented during development. The model does not independently establish depot formation, local tissue response, systemic exposure, dose reliability, or performance after scale-up.

Drug–excipient compatibility prediction adds a further formulation-search function by using molecular descriptors, learned representations, or ensemble models to estimate interaction risk before extensive physical testing. Such approaches can help prioritize excipient choices and direct confirmatory experiments, particularly when the possible combination space is large [11]. Yet compatibility is conditional on concentration, moisture, temperature, processing history, packaging, storage duration, and the analytical criterion used to define an interaction. A model trained on pairwise labels may therefore miss incompatibilities that emerge only in a multicomponent formulation or under a specific manufacturing and storage condition. Across formulation prediction, nanocrystal screening, long-acting injectable design, and compatibility assessment, the defensible conclusion is that artificial intelligence can make formulation search more selective. It does not remove the need for experimental verification, nor does it convert an intermediate formulation prediction into evidence of therapeutic exposure.

Modeling Material Behavior, Release, Transport, and Biodistribution

Material behavior is the first major transition beyond composition-level screening because a formulation must generate a reproducible physical state before it can control drug release. Artificial-intelligence models in this domain may represent composition, porosity, geometry, polymer characteristics, drug properties, manufacturing variables, and sampling time as predictors of dissolution or release behavior. Recent tablet-focused work demonstrates that machine learning can predict dynamic release profiles and associated kinetic parameters from formulation information rather than reducing performance to a single terminal measurement [12]. This represents an important extension of formulation prediction because the model addresses time-dependent behavior. Nevertheless, the predicted curve remains an in vitro description generated under a defined assay. It does not independently establish gastrointestinal dissolution, absorption, local delivery, or systemic exposure, and the apparent kinetic interpretation remains conditional on the experimental design and represented formulation space.

Platform-specific biomaterial studies further show how artificial intelligence can clarify relationships among scaffold composition, degradation, and release. Supervised learning applied to acetalated-dextran nanofibers has been used to model time-dependent drug release from experimentally characterized constructs [13]. Such work is valuable because the model is anchored to measured material behavior and can help identify which formulation or scaffold characteristics most strongly influence release within that platform. However, a model derived from one polymer family, fabrication process, and release environment cannot be assumed to describe microspheres, implants, hydrogels, lipid systems, or other nanofibers. The scientific contribution is therefore local rather than universal: artificial intelligence may support interpretation and prediction within a defined material system, while transfer to a new geometry, degradation pathway, drug-loading mechanism, or physiological condition requires new evidence.

Transport and biodistribution introduce an additional layer of complexity because formulation properties interact with administration route, protein adsorption, vascular access, tissue architecture, cellular uptake, immune recognition, and clearance. Machine-learning models trained on preclinical nanoparticle studies indicate that particle and experimental descriptors contain predictive information about tissue distribution and tumor delivery in mice [14]. This evidence supports the use of artificial intelligence for preclinical prioritization and for identifying recurring relationships across heterogeneous nanoparticle studies. It does not establish that the same relationships will remain valid in humans, where physiological scale, disease heterogeneity, immune state, dose, and clinical administration conditions differ. Moreover, retrospective biodistribution datasets may encode laboratory practices and reporting conventions alongside biological signal, making species, route, and study provenance part of the applicability domain rather than incidental metadata.

Hybrid architectures attempt to move beyond statistical association by combining machine learning with physiologically based pharmacokinetic structure. An artificial-intelligence-assisted physiologically based pharmacokinetic model has been developed to predict nanoparticle delivery to tumors in mice, illustrating how learned relationships can support parameterization or refinement of a mechanistic disposition model [15]. The advantage of this approach is not that mechanism becomes proven, but that formulation descriptors, physiological compartments, and concentration–time behavior can be represented in one analytical system. Its limitations remain substantial: predictions depend on preclinical data, parameter assumptions, model identifiability, and the biological processes included in the structure. The manuscript therefore proposes a formulation-to-exposure translation arc in which material and biological models are treated as connected but separately validated layers. **Figure 1** presents the formulation-to-exposure ai translation arc, showing how the article's key components and boundaries are connected within modeling material behavior, release, transport, and biodistribution.

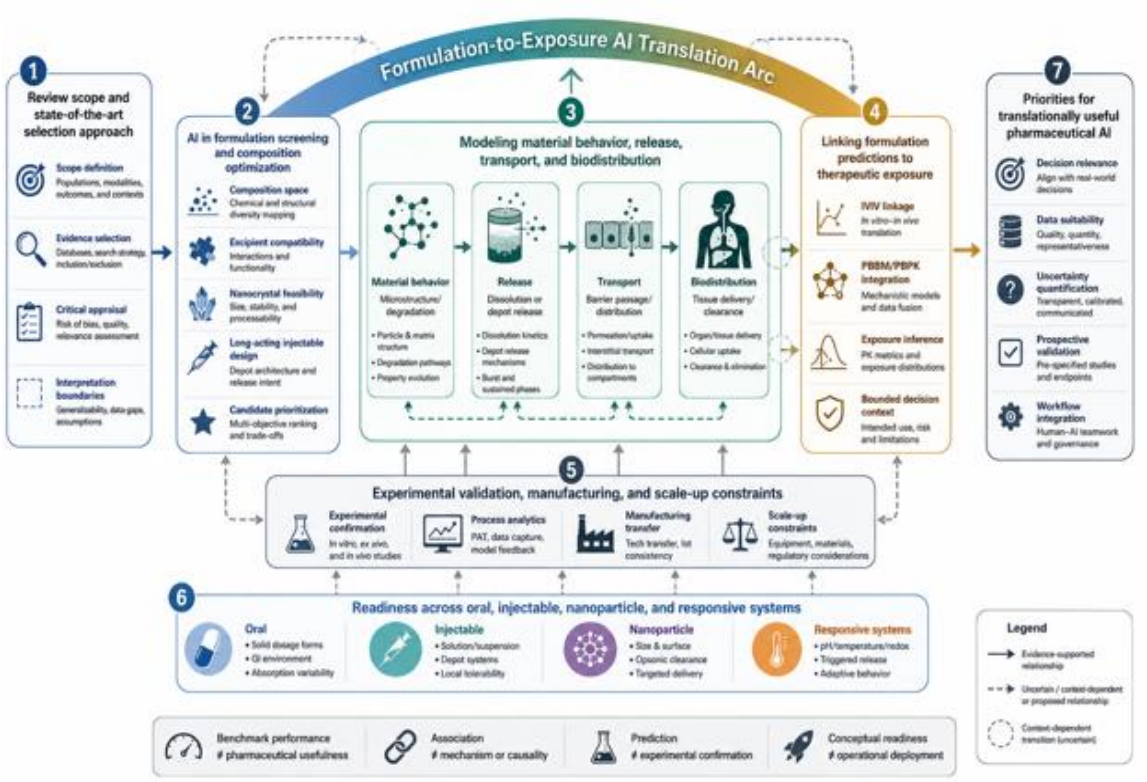

Figure 1. Formulation-to-Exposure AI Translation Arc.

The figure is an original conceptual synthesis that organizes the article's central contribution across review scope and state-of-the-art selection approach, AI in formulation screening and composition optimization, modeling material behavior, release, transport, and biodistribution, modeling material behavior, linking formulation predictions to therapeutic exposure, experimental validation, manufacturing, and scale-up constraints. Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, regulatory determination, clinical recommendation, or deployment-ready system.

Linking Formulation Predictions to Therapeutic Exposure

The transition from formulation prediction to therapeutic exposure requires an explicit account of how the delivered drug encounters physiological processes. For oral products, dissolution is only one component of a sequence that may also involve precipitation, degradation, gastric emptying, intestinal transit, regional fluid conditions, permeability, metabolism, and systemic disposition. Physiologically based absorption modeling provides a framework for connecting in vitro formulation measurements to these in vivo processes and for determining whether a dissolution method is biopredictive for a defined product and question [16]. This framework clarifies why release cannot be treated as a universal surrogate for therapeutic performance. The same dissolution profile may have different exposure consequences depending on permeability, dose, formulation type, gastrointestinal physiology, and the relationship between local concentrations and absorption.

Physiologically based biopharmaceutics modeling extends this logic by integrating drug properties, formulation characteristics, dissolution behavior, physiological variables, and pharmacokinetic processes within a context-of-use model. Reviews of its current use in oral drug-product development show that it can support formulation comparison, risk assessment, and scenario analysis when the relevant input data and qualification evidence are available [17]. Its scientific value lies in converting an isolated formulation prediction into a hypothesis about exposure under specified conditions. However, the presence of mechanistic compartments does not guarantee accuracy. Model behavior may be sensitive to uncertain solubility, precipitation, permeability, gastric or intestinal transit, and disposition parameters. Consequently, a credible exposure model requires transparent assumptions, sensitivity analysis, and validation against evidence relevant to the decision it is intended to support.

Regional absorption studies demonstrate why applicability must be evaluated at the level of specific physiological and formulation contexts. Physiologically based biopharmaceutics modeling of regional and colonic absorption in humans has shown that predictive performance can vary across compounds, permeability characteristics, and immediate-, extended-, or colon-targeted formulations [18]. This variability is not merely a technical inconvenience; it identifies where the formulation-to-exposure linkage is scientifically fragile. A model may reproduce one dosage form while failing when release is shifted to a different intestinal region or when absorption becomes more dependent on local physiology. Exposure linkage should therefore include explicit failure analysis rather than only global agreement with observed concentration–time behavior. Such

analysis can reveal whether uncertainty originates in the release model, physiological assumptions, absorption parameters, or the boundary conditions of the intended formulation.

Decision relevance becomes clearest when a model is qualified for a bounded pharmaceutical question. In immediate-release product development, physiologically based biopharmaceutics modeling has been used to connect dissolution behavior with exposure and to define a product-specific bioequivalence dissolution safe space [19]. This type of application differs fundamentally from generic prediction because the model is evaluated against a specified development objective and used to explore a constrained range of formulation performance. Even in this stronger setting, the resulting safe space is product- and context-dependent rather than universally transferable. The broader review interpretation is that therapeutic-exposure linkage should be treated as a distinct evidentiary gate. A formulation model becomes development-relevant only when its intermediate predictions are connected to an exposure question, qualified with appropriate data, and interpreted within a defined decision boundary.

Experimental Validation, Manufacturing, and Scale-Up Constraints

Experimental confirmation is the point at which computational prioritization begins to acquire pharmaceutical credibility. In manufacturing, however, validation must address more than whether a model predicts a laboratory endpoint. Continuous pharmaceutical production generates multivariate time-series data affected by material variability, equipment state, operating conditions, sensor behavior, and process dynamics. Deep-learning applications in continuous solid-dosage manufacturing demonstrate that such data can support process monitoring and prediction of quality-related attributes within a defined production environment [20]. This evidence establishes operational potential, but not automatic transferability. A model trained on one line may encode equipment-specific relationships and may require requalification after changes in scale, sensor configuration, raw-material source, process range, or control strategy.

Artificial neural networks used within process analytical technology offer a related route to real-time estimation of process state and product quality. The pharmaceutical PAT literature shows that neural models can extract complex relationships from spectroscopic and process measurements that may be difficult to represent with simple linear calibration [21]. Their readiness nevertheless depends on lifecycle considerations that are often secondary in model-development reports. Calibration transfer, reference-method quality, sensor drift, missing data, process changes, and model updating can alter performance after initial validation. A manufacturing model should therefore be evaluated as a maintained component of a quality system rather than as a static algorithm. Accuracy during development is necessary, but sustained performance under realistic process variation is the more relevant criterion.

Generative approaches add virtual experimentation by reconstructing or synthesizing representations of pharmaceutical microstructure. Generative artificial intelligence has been applied to create digital solid-dosage structures for formulation optimization and particle-engineering analyses [22]. Such models may permit exploration of structure–property relationships without manufacturing every hypothetical configuration and may support simulation of how porosity, packing, particle arrangement, or other structural features influence performance. Yet visual or statistical similarity between generated and observed structures does not establish that the digital product can be manufactured reproducibly. Nor does agreement in a simulated property establish physical equivalence, stability, or bioavailability. Generative formulation models therefore remain hypothesis-generating unless digital structures are connected to independently produced materials and experimentally confirmed product attributes.

Closed-loop experimentation provides stronger evidence because the model influences prospective experimental selection and is updated using newly generated results. A semi-self-driven robotic formulator combining liquid handling, measurement, and Bayesian optimization has demonstrated efficient discovery within a bounded medicine-formulation problem [23]. This type of study moves beyond retrospective benchmarking by testing whether algorithmic selection can guide real experiments. Its translational interpretation must still remain narrow: performance for one molecule, objective, robotic platform, and laboratory does not establish general superiority across formulation classes or scales. Prospective comparisons with expert-guided development, design-of-experiments strategies, and alternative optimization methods are needed. Scale-up also introduces mixing, heat and mass transfer, hold times, equipment geometry, sterility, containment, and supply-chain constraints that may not be represented in laboratory optimization.

Readiness Across Aral, Injectable, Nanoparticle, and Responsive Systems

Oral solid-dosage development currently offers the broadest and most differentiated set of artificial-intelligence applications among the modalities considered here. Machine learning has been applied to preformulation, excipient selection, manufacturability, dissolution, process monitoring, and product-quality prediction across oral dosage-form development [24]. This breadth reflects the availability of established tests, historical development records, standardized unit operations, and relatively mature mechanistic biopharmaceutic models. It does not mean that oral artificial intelligence is uniformly ready. Retrospective formulation prediction may remain immature even when process analytics are operationally useful, while exposure models may be decision-relevant only for drugs and products with sufficiently characterized absorption mechanisms. Readiness must therefore be assigned to a task and context rather than to the oral modality as a whole.

Long-acting injectable and implantable products impose a different set of constraints because formulation performance is distributed across manufacturing, administration, depot formation, release duration, local tolerability, device characteristics, patient acceptability, and product retrieval or reversibility. Industrial analyses of these platforms emphasize that successful

translation requires integration of patient-centered, product, device, and manufacturing considerations [25]. An artificial-intelligence model that optimizes polymer composition or predicted release may address only one component of this system. Readiness would additionally require evidence that the formulation can be produced consistently, administered through an acceptable device, maintain stability, achieve the intended exposure duration, and remain clinically practical. The relevant development objective is therefore multi-criteria and may involve trade-offs that cannot be represented by a single predicted endpoint.

Lipid nanoparticles provide some of the strongest prospective evidence that machine learning can influence experimental candidate discovery. Machine-learning-guided combinatorial chemistry has accelerated the identification of ionizable lipids for messenger-RNA delivery and produced candidates that were subsequently evaluated experimentally [26]. This establishes more than retrospective correlation because algorithmic prioritization contributed to the selection of testable materials. Nevertheless, delivery activity remains conditional on cargo, route, dose, cell type, organ, disease context, and assay. A lipid active in one experimental setting may not retain the same performance or safety profile in another. Manufacturing reproducibility, storage, particle heterogeneity, immune effects, and clinical administration introduce further gates between material discovery and routine therapeutic use.

Responsive systems have the least uniform readiness because their defining behavior depends on a trigger that must be accessible, controllable, safe, and coupled reproducibly to drug release. Photoresponsive delivery research illustrates progress in materials that react to external stimulation while also revealing persistent challenges involving light penetration, off-target exposure, material toxicity, trigger dose, device integration, and physiological variability [27]. Similar concerns apply to systems activated by pH, enzymes, redox state, temperature, ultrasound, magnetic fields, or other endogenous and external signals. The review therefore proposes a modality-sensitive readiness interpretation. Oral systems possess the most established data and modeling infrastructure; long-acting systems require integrated patient, device, and duration evidence; nanoparticle systems show growing prospective discovery capability but uncertain biological transfer; and responsive systems retain substantial trigger and safety constraints. These are interpretive boundaries, not validated or regulatory maturity classifications.

Priorities for Translationally Useful Pharmaceutical AI

The first priority is to redefine performance around pharmaceutical decisions rather than isolated predictive metrics. Critical analyses of pharmaceutical artificial intelligence converge on three linked requirements: models must address questions that can alter scientific action, use data that are suitable for the intended task, and provide explanations whose meaning is not confused with mechanism or causality [28–30]. A formulation model should therefore be assessed by whether it changes candidate selection, experimental allocation, formulation range, or risk management relative to credible alternatives. Data suitability should include provenance, negative results, experimental conditions, process history, route, and applicability domain. Interpretability should identify model dependence and support scientific scrutiny, while avoiding claims that feature attribution demonstrates a biological or material mechanism.

The second priority is prospective, comparative validation across the full decision chain. Recent assessments of artificial intelligence in drug discovery conclude that substantial technical progress has not yet translated into uniform routine readiness because evidence of reproducibility, prospective value, workflow integration, and advantage over established practice remains limited [31]. For drug-delivery development, prospective validation should test not only whether a prediction is accurate, but whether it improves an experiment or decision. Comparators may include expert selection, mechanistic modeling, conventional design of experiments, or existing manufacturing controls. External validation should also reflect the anticipated use case: a new chemical series, excipient family, polymer batch, manufacturing line, laboratory, administration route, or biological context.

The third priority is the construction of linked, uncertainty-aware models rather than disconnected predictors. A translationally useful architecture may require separate modules for composition, material structure, release, transport, biodistribution, exposure, and manufacturing, with uncertainty propagated across transitions. Such a system should preserve distinctions between measured variables, learned associations, mechanistic assumptions, and proposed causal relationships. Calibration is particularly important when a model extrapolates beyond familiar formulation or physiological conditions. The review proposes that applicability-domain analysis, uncertainty decomposition, and explicit stop rules should accompany model outputs so that experimental decisions are not driven by apparently precise predictions generated in poorly represented regions.

The fourth priority is evidence-gated implementation. Data governance, model versioning, assay standardization, process drift monitoring, human oversight, and context-of-use documentation should be developed alongside algorithmic performance. Multimodal data infrastructures should capture formulation composition, processing history, material characterization, biological environment, exposure, and failed experiments rather than only successful endpoints. Research should also evaluate patient, device, administration, safety, and manufacturing constraints early enough to prevent optimization toward products that are computationally attractive but operationally unusable. **Table 2** organizes the evidence, constructs, and interpretation boundaries needed to develop priorities for translationally useful pharmaceutical ai within the article's central argument.

Table 2. Evaluation, implementation, and research priorities arising from From Formulation Search to Therapeutic Exposure the Changing Role of Artificial Intelligence

Approach or Application	Data and Task Context	Evaluation Practice	Evidence Maturity	Translational Limitation	Review Interpretation

Formulation Screening and Compatibility Prediction	Composition, molecular, excipient, and historical formulation records	Internal validation supplemented by chemical, temporal, and external formulation holdouts	Retrospective benchmark to experimentally anchored	Label inconsistency, sparse negative results, and narrow formulation domains	Appropriate for candidate prioritization when applicability boundaries are explicit
Release-Profile Modeling	Formulation, material, process, and time-dependent in vitro data	Full-profile validation, kinetic plausibility checks, and prospective formulation testing	Platform-specific experimental capability	Assay dependence and uncertain in vitro–in vivo relevance	A useful intermediate model that requires exposure linkage
Nanoparticle Biodistribution Prediction	Particle descriptors, route, dose, animal, tissue, and study-level variables	Study-level external validation, species-aware testing, and uncertainty calibration	Preclinical retrospective capability	Interstudy heterogeneity and weak human translation	Suitable for preclinical prioritization, not direct clinical inference
Hybrid Artificial Intelligence and Mechanistic Modeling	Learned formulation relationships integrated with PBPK or PBBM structure	Parameter sensitivity, identifiability analysis, external exposure validation, and context-of-use qualification	Mechanistically anchored and case-dependent	Dependence on assumptions, input quality, and physiological coverage	Potential bridge from intermediate formulation outcomes to bounded exposure questions
Manufacturing Analytics and Pat	Multivariate process, sensor, raw-material, and quality data	Temporal validation, drift testing, calibration transfer, and cross-line or cross-site assessment	Process-demonstrated in defined settings	Equipment dependence and lifecycle maintenance burden	Operational usefulness requires continuing validation rather than one-time model acceptance
Generative Digital Formulation Models	Images, microstructures, material representations, and simulated product attributes	Comparison with independently manufactured structures and experimentally measured properties	Digital proof of concept	Realism does not establish manufacturability or equivalence	Valuable for hypothesis generation and virtual exploration
Closed-Loop Robotic Formulation	Automated experiments, predefined objectives, and sequential optimization	Prospective comparison with expert and design-of-experiments baselines	Prospective but narrowly bounded	Limited molecules, objectives, platforms, and scale-up evidence	Strong evidence of search efficiency within a specified task, not routine general deployment
Oral Drug-Product Modeling	Preformulation, dissolution, absorption, process, and product data	Endpoint-specific external validation and qualified biopharmaceutic linkage	Heterogeneous; comparatively mature in selected tasks	Variable data quality and product-specific exposure mechanisms	Readiness should be assigned per task, not to the oral modality universally
Long-Acting Injectable and Implantable Optimization	Polymer, drug, device, process, release-duration, and patient-use variables	Prospective release, manufacturability, device, tolerability, and exposure validation	Emerging platform-specific capability	Long duration, depot behavior, device constraints, and patient acceptability	Requires integrated product and patient objectives beyond release prediction
Lipid-Nanoparticle Discovery	Lipid structures, composition, process, cargo, and biological assay data	Prospective synthesis and testing across cargo, route, and biological contexts	Prospective experimental discovery capability	Assay, cargo, organ, route, safety, and manufacturing dependence	Demonstrates discovery value while leaving broader therapeutic readiness unresolved
Responsive Drug-Delivery Systems	Trigger-sensitive materials, physiological environment, device input, and release response	Trigger–dose–release validation, safety envelopes, and clinically relevant penetration testing	Conceptual to preclinical	Trigger variability, penetration, safety, and control	High-potential but high-burden domain requiring modality-specific evidence
Translational Implementation	Linked formulation, material, biological, exposure, manufacturing, and decision data	Prospective decision-impact studies, governance audits, version control, and lifecycle monitoring	Proposed evidence-gated framework	Lack of common standards and limited routine-use evidence	The proposed priority is validation of the full decision chain, not expansion of benchmark complexity

Table note: Evidence-maturity descriptions are original interpretive categories proposed for this review. They are not validated scores, regulatory classifications, or universal rankings of delivery modalities.

Conclusion

Artificial intelligence is changing advanced drug-delivery development by making formulation search more selective, material behavior more computable, experimental design more adaptive, and exposure questions more accessible to integrated modeling. Its most defensible current contribution is not autonomous formulation discovery or universal prediction, but structured prioritization within bounded pharmaceutical domains. The original contribution of this review is the proposed formulation-to-exposure translation arc, which separates composition prediction, material and release behavior, transport and biodistribution, therapeutic exposure, manufacturing evidence, and development decisions into connected but independently validated stages. This interpretation prevents benchmark performance from being treated as proof of mechanism, manufacturability, clinical utility, or routine readiness. The evidence base supports growing capability in formulation prediction, experimentally anchored release modeling, selected preclinical biodistribution tasks, mechanistic biopharmaceutic linkage, process analytics, and prospective closed-loop search. It remains limited by sparse and heterogeneous data, uncertain applicability domains, weak cross-species and cross-scale transfer, incomplete uncertainty characterization, and insufficient prospective comparison with established pharmaceutical practice. Translational progress will therefore depend less on larger

isolated models than on decision-relevant data, prospective experimental confirmation, mechanistically coherent exposure linkage, lifecycle manufacturing validation, and modality-specific implementation criteria. The proposed arc and maturity distinctions should be regarded as a framework for critical organization and future testing rather than as a validated predictive, clinical, regulatory, or deployment system.

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