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# *Advanced Pharmaceutical Formulations across Scales: A Scoping Review of Digital Design, Continuous Manufacturing, and Patient-Centric Dosage Forms*

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**ABSTRACT**

*Advanced pharmaceutical formulations increasingly arise through interactions among material science, computational design, manufacturing technology, biopharmaceutic modelling, and patient-use requirements. This scoping review maps the concepts, technologies, evidence types, development stages, and translational interfaces represented across the literature. A PRISMA-ScR-compatible and JBI-informed approach defined broad mapping questions, eligibility boundaries, information sources, screening logic, data-charting fields, taxonomy construction, and descriptive thematic synthesis. The resulting framework distinguishes printed, carrier-based, long-acting, stimuli-responsive, and patient-tailored dosage forms from enabling methods including machine learning, mechanistic dissolution modelling, physiologically based biopharmaceutics modelling, continuous processing, process analytical technology, and unit-level verification. Evidence is unevenly distributed across scales. Laboratory formulation and technical-feasibility studies are prominent, whereas prospective model validation, manufacturing transfer, population-specific excipient qualification, human-factors evaluation, clinical implementation, and integration with care workflows are less consistently represented. Computational performance, analytical similarity, manufacturing control, patient acceptability, bioavailability, and therapeutic consequence therefore remain distinct evidence categories rather than interchangeable indicators of maturity. Principal gaps concern interoperable data, transparent model assumptions, external validation, cross-platform comparability, stability and scale-up evidence, flexible quality systems, and methods connecting patient requirements to formulation and manufacturing decisions. The review provides an evidence-bounded map of advanced formulations as cross-scale pharmaceutical systems without assuming that technical novelty establishes clinical, regulatory, or implementation readiness.*

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

Advanced pharmaceutical formulation is no longer defined only by selecting an active ingredient, excipients, and a conventional dosage form. Development may involve predictive models, digitally specified geometries, engineered carriers, long-acting depots, stimuli-responsive release, integrated manufacturing lines, real-time analytical control, and products tailored to particular populations or administration contexts. These technologies operate from molecular interactions and microstructure through equipment behaviour, product quality, supply,

administration, and patient experience. The central problem is whether evidence remains coherent across design, production, bioavailability, quality assurance, and use.

A scoping-review design is appropriate because the literature is heterogeneous in terminology, formulation class, data type, experimental system, intended application, and validation strategy. Rather than estimate pooled effects or rank technologies, the review asks what has been studied, how evidence can be classified, which development stages are represented, and where conceptual or implementation gaps remain. PRISMA-ScR provides the reporting structure for explaining rationale, eligibility, information sources, selection, charting, and synthesis [1]. Updated JBI guidance supports broad concept–context–source questions, iterative charting, and descriptive or thematic presentation when the purpose is to map a complex field [2].

Three domains show why cross-scale synthesis is needed. Computational pharmaceutics connects formulation data, mechanistic knowledge, and prediction; continuous manufacturing integrates material flow, unit operations, sensing, and control; personalized delivery linked with digital health introduces traceability, administration, and patient interaction. These domains are complementary, but they are often developed as separate technical trajectories rather than as components of one pharmaceutical pathway [3–5].

This review maps advanced formulations across material, dosage-form, process, modelling, manufacturing, and patient-use scales. It classifies technologies and enabling methods, examines how evaluation and validation are addressed, and identifies interfaces where promising technical evidence may fail to translate into robust pharmaceutical utility. Personalization is treated as a system involving product definition, flexible manufacture, provision, clinical decision-making, administration, and patient participation rather than dose customization alone [6]. The contribution is an evidence-bounded taxonomy and integration framework, not a claim of exhaustive coverage, uniform validation, clinical superiority, regulatory acceptance, or deployment readiness.

*Scoping-review objectives and protocol*

The protocol addressed six mapping questions: which concepts, technologies, data types, and application settings have been studied; how the literature should be classified and charted; which methods and development stages are represented; how evaluation, validation, and translation are treated; which concepts or contexts are missing or inconsistently defined; and what research agenda emerges.

The protocol used a concept–context–source structure. The concept included pharmaceutical formulation, dosage-form engineering, excipient compatibility, stability, bioavailability-related design, long-acting products, adaptive release, digital formulation development, continuous manufacturing, and patient-centric dosage forms. Contexts included laboratory formulation, computational development, process design, manufacturing, analytical verification, translational development, point-of-care production, and patient use. Eligible sources included primary studies, methodological articles, translational frameworks, and reviews supporting a specific claim or synthesis element.

Because the review did not estimate intervention effects, a conventional risk-of-bias score was not used to exclude evidence according to an effectiveness hierarchy. Appraisal instead concerned relevance and interpretability: directness of fit, system or population studied, method, outcome, validation stage, translation context, and limitations. Computational prediction, analytical verification, laboratory feasibility, manufacturing demonstration, acceptability, and clinical implementation were charted as different evidence forms. This prevented performance in one domain from being treated automatically as evidence of performance in another.

*Eligibility criteria and search strategy*

Eligible publications were peer-reviewed journal articles from the defined contemporary evidence period, published in journals verified as first quartile in a relevant category where verification was available, and carrying a verifiable DOI. Sources had to address at least one article-specific domain and provide extractable information assignable to a synthesis question, paragraph claim, taxonomy category, validation distinction, table cell, figure element, or translational boundary.

Sources were excluded when they were not peer-reviewed journal articles, lacked verifiable metadata, fell outside eligibility boundaries, or addressed an adjacent topic without direct contribution to the review questions. Conference papers, unreviewed preprints, books, theses, websites, policy pages, regulatory webpages, software documentation, repositories, and promotional commentary were not treated as included scientific evidence.

Information sources included bibliographic databases, publisher records, journal platforms, DOI metadata services, and public journal-ranking profiles. Search concepts combined title variants with pharmaceutical formulation, dosage form, excipient compatibility, process design, stability, bioavailability, long-acting

formulation, patient-centric dosage form, continuous manufacturing, digital design, adaptive release, and formulation translation. These were paired with prediction, modelling, external validation, analytical verification, scale-up, process control, implementation, human factors, and methodological limitations. Terms were refined iteratively to accommodate vocabulary differences across pharmaceutics, drug delivery, manufacturing science, biopharmaceutics, and digital health.

*Study selection and data-charting procedure*

Selection proceeded through duplicate identification, title and abstract assessment, full-text eligibility review, and documentation of exclusion reasons. Screening first tested formal eligibility and then whether a source could support a precise review element. A paper was not retained merely because it discussed an advanced technology broadly; it had to contribute extractable evidence on a defined formulation system, method, manufacturing operation, validation stage, patient-use attribute, limitation, or translation problem.

Data charting recorded source type, population or technical system, formulation concept, application context, data modality, method, outcome or capability, validation stage, key finding, limitation, and synthesis role. Development scale was charted separately to distinguish molecular or material evidence, dosage-form evidence, unit-operation and process evidence, integrated-manufacturing evidence, analytical and model-validation evidence, human-factors evidence, and clinical or implementation evidence.

Synthesis used descriptive mapping and structured thematic comparison rather than meta-analysis. Evidence was organized into formulation classes, digital design functions, continuous and adaptive manufacturing, patient-centric attributes, cross-scale interfaces, and validation layers. Contradictory or incomplete findings were represented through limitations, rival explanations, and boundary conditions, not numerical scores. No evidence-density measure, pooled estimate, readiness index, or quality grade was calculated. The taxonomy is an original review instrument, not a validated ontology or decision tool.

*Taxonomy of formulation technologies and development scales*

Advanced technologies can be classified by pharmaceutical function, scale of critical attributes, and evidence needed for evaluation. Additive-manufacturing platforms illustrate this multidimensionality: printer architecture, feedstock, energy input, geometric freedom, dose control, and release behaviour differ among methods [7]. “Three-dimensional printing” therefore denotes a family of manufacturing principles rather than one dosage-form class. Pharmaceutical significance depends on material compatibility, printability, content uniformity, stability, dissolution, administration, and production setting.

Carrier-based and long-acting formulations reveal comparable interactions among composition, microstructure, process, and biological context. Precision nanoparticles require coordinated control of physicochemical attributes, biological interactions, payload disposition, and manufacture; complex long-acting injectables depend on release mechanism, depot behaviour, microstructure, manufacturing consistency, and meaningful comparability; liposomes show how mixing, solvent handling, loading, downstream processing, and scale-up influence critical attributes [8–10].

Stimuli-responsive formulations constitute another branch. Reported triggers include pH, enzymes, redox conditions, temperature, light, and magnetic fields, yet sensitivity in a controlled model does not establish reliable adaptation in heterogeneous biological conditions [11]. The term adaptive release should therefore be reserved for systems whose signal detection, response reproducibility, payload release, and pharmacological consequence are evaluated within a defined context. Otherwise, evidence supports stimulus sensitivity rather than clinically meaningful adaptation.

Material-scale evidence concerns molecular interactions, excipient compatibility, solid state, rheology, and stability. Dosage-form evidence concerns dose accuracy, mechanics, release, handling, and administration. Process evidence examines feeding, mixing, deposition, drying, residence time, and control. Translational evidence addresses bioavailability, comparability, population suitability, supply, and use. The taxonomy combines technology class with evidence layer and intended decision without ranking platforms.

**Table 1** organizes the eligibility, charting constructs, uncertainties, and interpretation boundaries used across the review.

**Table 1.** Scoping-review eligibility and data-charting framework for Advanced Pharmaceutical Formulations across Scales.

| Evidence domain or review construct | Review question | Eligible evidence type | Key extraction fields | Appraisal or relevance criterion | Synthesis role | Main limitation | Interpretation boundary |
|---|---|---|---|---|---|---|---|
| **Review methodology** | How should a heterogeneous formulation field be mapped transparently? | Scoping-review reporting and conduct guidance | Objectives, eligibility, sources, selection, charting, synthesis | Direct applicability to scoping-review conduct | Defines the review architecture [1] | Reporting guidance does not determine substantive scientific relevance | Methodological transparency does not establish exhaustive coverage |
| **Concept–context–source boundaries** | Which formulation concepts, settings, and source types are relevant? | Methodological guidance and article-specific operational definitions | Concept, context, source type, unit of inclusion | Alignment with the review questions | Structures eligibility and charting [2] | Categories require iterative refinement | The framework is an original review instrument, not a validated ontology |
| **Additive dosage-form manufacture** | Which digitally fabricated dosage forms and process classes are represented? | Platform reviews and primary formulation studies | Printing method, feedstock, geometry, dose, release, product testing | Extractable formulation or manufacturing evidence | Maps digitally specified dosage forms [7] | Platform terminology can conceal major process differences | Technical printability is not equivalent to pharmaceutical utility |
| **Carrier-based formulations** | How are material attributes connected to delivery and translation? | Mechanistic reviews and formulation studies | Composition, size, surface, loading, biological context, manufacture | Direct evidence linking attributes to performance | Maps nanoparticle and liposomal classes [8] | Preclinical performance may be model-dependent | Carrier engineering alone cannot establish clinical benefit |
| **Long-acting formulations** | Which product attributes govern sustained exposure or depot behaviour? | Product-development and translation literature | Microstructure, release mechanism, manufacturing consistency, comparability | Evidence relevant to duration, quality, or translation | Distinguishes long-acting products from immediate-release forms [9] | In vitro similarity may not explain in vivo behaviour | Duration alone does not establish adherence or therapeutic improvement |
| **Manufacturing-sensitive carriers** | How does the production route affect product attributes? | Process reviews and scale-up studies | Mixing, solvent handling, loading, downstream processing, stability | Specific connection between process and critical attributes | Connects formulation and manufacturing scales [10] | Cross-platform transferability is limited | A scalable operation must still preserve product-specific quality |
| **Stimuli-responsive release** | Which triggers and response mechanisms have been examined? | Mechanistic, preclinical, and translational studies | Trigger, response mechanism, release, model system, validation stage | Demonstrated link between stimulus and formulation response | Maps adaptive-release concepts [11] | Biological signals may be variable or spatially heterogeneous | Trigger response does not alone establish pharmacological adaptation |
| **Cross-scale translation** | What evidence connects design, manufacture, product | Primary, methodological, human-factors, and implementation studies | Interface, validation stage, supported decision, | Evidence must identify a transition between scales | Supports later integration and maturity synthesis | Interfaces are studied unevenly | Absence of evidence at one interface cannot be replaced by evidence from another |

| | |
|---|---|
| quality, and use? | unresolved boundary |

**Figure 1** presents the original conceptual synthesis for scoping-review map of advanced formulation technologies, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

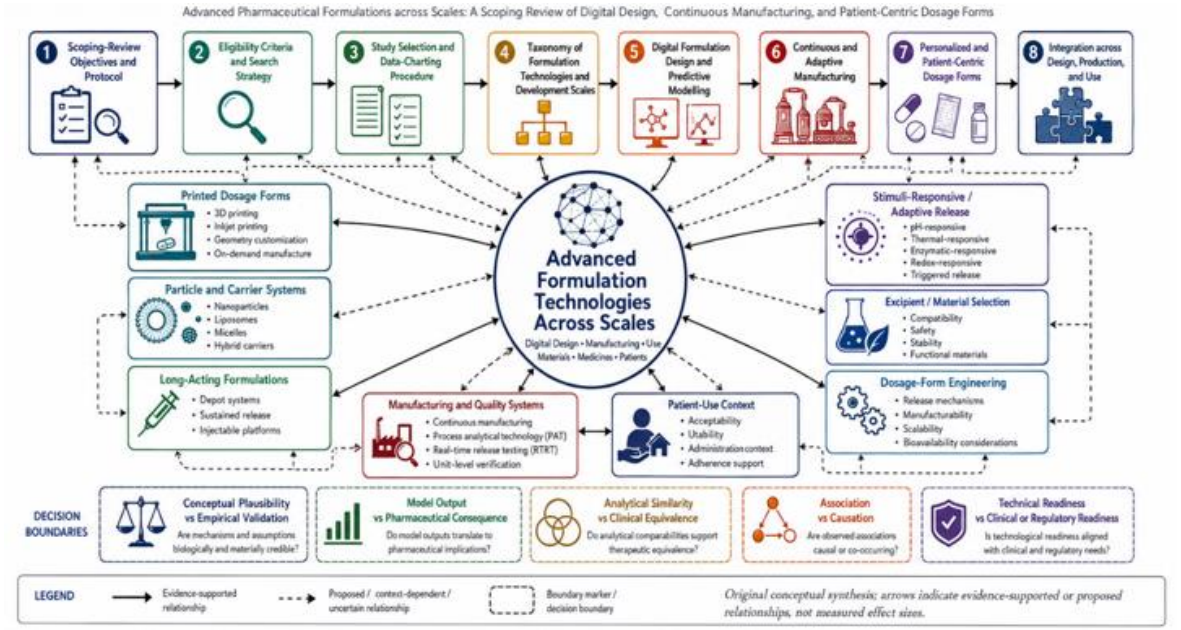


**Figure 1.** Scoping-Review Map of Advanced Formulation Technologies.

The figure is an original conceptual synthesis developed for "Advanced Pharmaceutical Formulations across Scales: A Scoping Review of Digital Design, Continuous Manufacturing, and Patient-Centric Dosage Forms." Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, clinical recommendation, regulatory determination, or deployment-ready system.

*Digital formulation design and predictive modelling*

Digital formulation design includes organizing knowledge, predicting attributes, optimizing experiments, simulating dissolution or absorption, and translating desired dose or release characteristics into manufacturable specifications. Machine learning can identify nonlinear associations and prioritize experiments when material, composition, process, and performance data are consistently structured [12]. Its value lies in supporting exploration, not replacing physical experiments, and depends on domain coverage, data quality, and prospective testing.

Primary computational studies illustrate both capability and boundary. Deep neural networks have predicted selected in vitro outcomes within curated datasets and outperformed comparator algorithms under reported conditions [13]. These findings establish dataset-specific performance, not universal accuracy. Internal partitions may preserve similarity between training and test examples, whereas a new active ingredient, excipient combination, manufacturing route, or laboratory may lie outside the learned domain.

Digital design can operate closer to the manufactured object. Automated workflows may convert individualized dose and release requirements into printable geometries and production instructions [14]. Geometry can influence mass, surface area, disintegration, and release, but digital specification remains only one component. Printable materials, process resolution, content uniformity, mechanical performance, stability, and analytical verification must remain acceptable.

Mechanistic and empirical models answer different questions. First-principles dissolution models seek to represent wetting, diffusion, disintegration, surface-area change, and mass transfer, whereas empirical models may describe associations without assigning physical meaning to every fitted parameter [15]. Mechanistic detail

does not guarantee accuracy, and strong fit does not prove mechanism. Assumptions, parameter identifiability, experimental conditions, and consequences of error require explicit reporting.

Physiologically based biopharmaceutics modelling extends prediction toward gastrointestinal behaviour, absorption, and exposure. Credible use requires a defined question, appropriate structure, traceable inputs, implementation verification, relevant validation, and a declared context of use [16]. A model adequate for formulation ranking may not support specification setting, manufacturing-change assessment, or prediction in another population. Computational performance, biopharmaceutic plausibility, experimental verification, and decision relevance should therefore be assessed separately.

*Continuous and adaptive manufacturing*

Continuous manufacturing connects material input, transformation, monitoring, and product output through integrated operations. An end-to-end demonstration linked synthesis, crystallization, filtration, drying, blending, and tableting within one sequence [17]. Such integration may reduce isolated scale transitions and provide richer process data, but one proof-of-concept line cannot establish universal scalability. Reaction kinetics, solid-state behaviour, powder flow, residence time, solvent systems, and equipment compatibility remain product-specific.

Local equipment features can influence downstream quality. Feed-frame geometry and configuration alter powder residence-time distribution, mixing, and tablet-output variation [18]. Disturbances may propagate through the line, and the quantity of affected material depends on flow dynamics. Residence-time analysis therefore informs diversion, sampling, traceability, and assessment of transitions between operating states.

Adaptive manufacturing should be distinguished from adaptive release. In manufacturing, adaptation may involve feedback control, fault detection, maintenance, or operating adjustments. Condition-based maintenance can use equipment and process signals to anticipate degradation and support interventions [19]. Its benefit depends on sensor reliability, representative failure data, diagnostic specificity, and transfer across configurations.

Real-time release testing is a control strategy rather than one instrument. It requires defined critical quality attributes, representative measurements, suitable sampling, validated sensors or soft sensors, model maintenance, data governance, and controlled decision procedures [20]. A signal becomes release-relevant only when its relationship to product quality is demonstrated for the intended process. Continuous operation therefore gains pharmaceutical value through the integrity of the entire measurement-and-control system.

*Personalized and patient-centric dosage forms*

Patient-centric design recognizes that a technically valid dosage form may remain unsuitable for a user or care setting. Selection must balance acceptability, administration safety, dose flexibility, formulation feasibility, and access, particularly for paediatric and geriatric populations [21]. Size, swallowing ability, manipulation, taste, dosing frequency, packaging, caregiver involvement, and available strengths may all affect use.

Excipient choice links formulation performance with population suitability. An excipient may support solubility, stability, manufacture, taste masking, or release, yet safety cannot always be inferred from adult precedent when exposure or developmental physiology differs [22]. Compatibility also has distinct dimensions: chemical and physical compatibility with the active ingredient, process compatibility, shelf-life stability, and safety in the intended population.

Human-factors evidence can identify preferences invisible to conventional tests. An exploratory study of printed medicines showed that shape, size, colour, and familiarity influenced perceptions and handling [23]. Such observations support user involvement, but acceptability is context-dependent. Preference in healthy participants does not automatically predict swallowing success, adherence, bioavailability, or benefit in patients.

Printed gummies show how dose customization and sensory-oriented design may coexist [24]. Appeal does not remove requirements for uniformity, stability, release, packaging, and safe administration. A pleasant dosage form may still be unsuitable for a high dose, unstable molecule, narrow therapeutic index, or unacceptable taste. Patient-centric formulation requires negotiated trade-offs rather than maximization of one preference.

**Table 2** organizes representative technologies, reported strengths, validation contexts, generalization concerns, and review interpretations.

**Table 2.** Concept, method, technology, or application taxonomy for Advanced Pharmaceutical Formulations across Scales.

| Method, platform, or | Representative application | Reported strength | Validation context | Generalization concern | Contradictory evidence | Evidence gap | Review interpretation |
|---|---|---|---|---|---|---|---|

| evidence category | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Additive manufacture** | Customized oral products | Flexible geometry, dose, and release [7] | Laboratory characterization | Printer and feedstock specificity | Flexibility may coexist with limited throughput | Stability and transfer | A family of methods, not one technology |
| **Nanoparticle or liposomal carriers** | Engineered delivery | Tunable composition and biological interaction [8] | Mainly preclinical or product-specific | Model-dependent biological identity | Laboratory targeting may not translate | Reproducible manufacture and comparative evidence | Design must connect biology with production |
| **Long-acting formulations** | Sustained exposure | Extended release [9] | Product-specific analytical and biopharmaceutic testing | Different depot mechanisms | Similar in vitro profiles may diverge in vivo | Mechanistic comparability | Duration alone does not establish benefit |
| **Stimuli-responsive systems** | Triggered release | Conditional release control [11] | Mostly experimental models | Variable biological triggers | Simplified-media response may not persist in vivo | Realistic external validation | Sensitivity is not validated adaptation |
| **Machine-learning design** | Prediction and experiment selection | Nonlinear modelling [12] | Mainly retrospective datasets | Dataset shift | High internal accuracy may transfer poorly | Prospective multi-site testing | Decision support depends on data and context |
| **Continuous manufacture and RTRT** | Integrated tablet production | Connected flow, sensing, and control [20] | Product- and line-specific implementation | Equipment–material dependence | Rapid measurement may not justify release | Lifecycle model governance | A quality system, not uninterrupted machinery |
| **Patient-centric design** | Age-appropriate or individualized products | Better fit with administration needs [21] | Formulation and exploratory human-factors studies | Population and setting variability | Preference may not improve adherence | Outcome and workflow evidence | Product and use evidence must be integrated |

*Integration across design, production, and use*

Integration becomes visible when digital design connects to realistic manufacture and verification. Combining three-dimensional printing with injection moulding can separate customized tooling from faster replication of dosage units [25]. This approach bridges one-off manufacture and conventional production, yet economic viability, cleaning, dimensional control, material compatibility, batch definition, and quality-system integration remain context-dependent.

Quality verification is another interface. Non-destructive spectroscopy has estimated the content of two drugs within printed polyprintlets [26]. Unit-level verification could be valuable when individualized products differ in dose or composition because destructive sampling may not represent each unique unit. Nevertheless, calibration validity, interference, instrument performance, acceptance criteria, and model maintenance must be established. Analytical prediction under experimental conditions is not automatically a validated release decision.

Aqueous inkjet printing links formulation properties, deposition behaviour, substrate interaction, drying, dose uniformity, and dissolution [27]. Each interface creates a failure point. An ink may be chemically suitable but difficult to jet; a deposited pattern may be precise but unstable during drying; a visually intact unit may fail content or release requirements.

Integration also extends to administration. A dosing device for individualized warfarin oral films shows how a dosage form and use-stage tool can constitute one dosing system [28]. Performance concerns not only drug content but whether the intended dose can be prepared accurately within the target workflow. Usability, error, storage, labelling, traceability, and communication may influence exposure. Product boundaries should include interfaces most likely to alter the administered dose.

*Evidence distribution and maturity assessment*

Evidence is unevenly distributed across development layers. Three-dimensional printing provides a clear example: formulation feasibility, geometric customization, and laboratory characterization are widely represented, while

clinical applications, quality-system integration, regulation, and routine point-of-care manufacture are less mature [29]. This imbalance shows that technical feasibility often precedes reproducible implementation.

Maturity can be described as a chain of conceptual plausibility, technical feasibility, verification, fit-for-purpose validation, translation, and implementation. Printed-pharmaceutical reviews identify gaps between innovation and real-world use, while PBBM reports distinguish applications and evidentiary demands and emphasize consistent development, validation, application, and reporting [29–31]. This chain is a qualitative synthesis, not a readiness score, and the strongest demonstrated layer may differ by product, model, decision, and jurisdiction.

Quality by Digital Design seeks to connect data, models, formulation knowledge, manufacturing, sustainability, and patient requirements [32]. Its importance lies in treating digital tools as components of a development system rather than isolated prediction engines. Interoperability, governance, lifecycle maintenance, physical experimentation, and decision responsibility remain necessary.

Evidence maturity depends on the decision being supported. A laboratory release profile may compare prototypes but not establish bioavailability. Internal model accuracy may support method development but not prospective formulation selection. Analytical verification may support a quality attribute but not clinical equivalence. Acceptability may inform design but not prove adherence. Maturity should therefore be interpreted through alignment of evidence, context, and decision consequence.

**Table 3** maps cross-study patterns, rival explanations, rigour concerns, implications, and research priorities without assigning numerical grades.

**Table 3.** Evidence distribution, validation maturity, and translational coverage in Advanced Pharmaceutical Formulations across Scales**.**

| Cross-study pattern or configuration | Context or boundary condition | Mechanism or explanatory factor | Observed or reported outcome | Rival explanation | Certainty or rigour concern | Implication | Research priority |
|---|---|---|---|---|---|---|---|
| **Technical flexibility with limited translation** | Printed individualized products | Digital geometry enables variation | Diverse prototypes [29] | Publication favours novelty | Heterogeneous platforms | Feasibility is not readiness | Link quality, workflow, and clinical evaluation |
| **Strong internal prediction with uncertain transfer** | Machine-learning formulation studies | Algorithms learn available associations | Useful retrospective prediction [12] | Train–test similarity may inflate transfer | Small datasets and domain shift | External validity needs separate testing | Prospective multi-product validation |
| **Mechanistic plausibility with contextual credibility** | Dissolution and PBBM | Models connect product attributes with absorption | Support for selected quality questions [30] | Calibration may compensate for structural error | Parameter uncertainty | Context of use determines evidence needs | Transparent inputs and sensitivity analysis |
| **Integrated processing with line-specific evidence** | Continuous tablet manufacture | Connected operations control material flow | End-to-end feasibility [17] | Success may reflect favourable equipment and product | Limited cross-site replication | Scale-up is system transfer | Disturbance and transfer studies |
| **Real-time data without automatic release authority** | PAT and RTRT | Sensors and models provide timely information | Potential release support [20] | Signal may not represent final quality | Drift and sampling concerns | RTRT requires a validated decision system | Lifecycle governance |
| **Patient-oriented design without clinical consequence** | Personalized dosage forms | Size, taste, and geometry affect acceptability | Population-specific preferences [21] | Novelty or familiarity may influence preference | Exploratory human studies | Acceptability is not adherence | Target-population usability and outcome studies |
| **Emerging cross-scale** | Quality by Digital Design | Shared data may connect product, | Proposed integration | Organizational maturity may drive success | Limited end-to-end validation | Treat integration as | Interoperable data and |

| | | | | |
|---|---|---|---|---|
| **digital architecture** | process, and patient needs | framework [32] | socio-technical | prospective implementation |

*Research gaps and implementation priorities*

A central modelling priority is transparent parameterization. PBBM may combine physiological variables, active-ingredient properties, formulation inputs, dissolution behaviour, and assumptions about variability, yet confidence depends on input provenance and uncertainty [33]. Studies should distinguish measured, literature-derived, estimated, optimized, and assumed parameters; justify sensitivity ranges; and report how uncertainty affects the intended decision. Shared datasets are useful only when experimental conditions, product definitions, and quality controls are documented.

Validation requires separation among base-model qualification, software verification, product-specific calibration, external validation, and application testing. Validation criteria and datasets should reflect the question and consequence of error [34]. Cross-platform studies should test whether models remain credible with new active ingredients, dosage forms, laboratories, manufacturing sites, or populations. Similar principles apply to analytical models and soft sensors whose performance may change with materials, equipment, or operating conditions.

Implementation research must connect model-informed development with clinical and operational evidence. Broader PBBM application requires stronger case libraries, transparent communication, model-risk assessment, and defensible links between in vitro differences and in vivo consequences [35]. Point-of-care printing requires trial designs integrating manufacture, quality control, ethics, site capability, recruitment, and regulatory responsibility [36]. The priority is whether a formulation can be specified, verified, transferred, administered, and studied within its intended system.

**Figure 2** presents the original conceptual synthesis for cross-scale integration from digital design to patient use, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

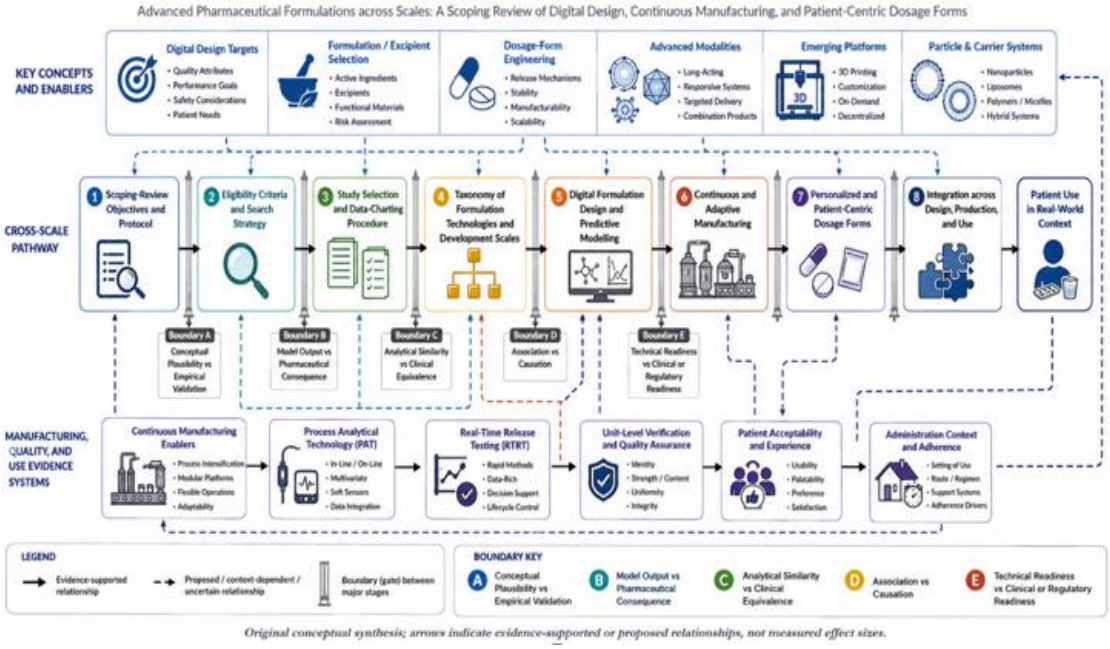


**Figure 2.** Cross-Scale Integration from Digital Design to Patient Use.

The figure is an original conceptual synthesis developed for "Advanced Pharmaceutical Formulations across Scales: A Scoping Review of Digital Design, Continuous Manufacturing, and Patient-Centric Dosage Forms." Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, clinical recommendation, regulatory determination, or deployment-ready system.

*Review limitations*

The review maps a deliberately bounded body of peer-reviewed evidence and is not an exhaustive inventory of every advanced formulation technology. Terminology varies across computational pharmaceutics, drug delivery,

manufacturing science, biopharmaceutics, personalization, and digital health. Scoping-review transparency does not eliminate these coverage limitations [1].

The evidence is heterogeneous in active ingredient, composition, dosage form, equipment, scale, model system, data modality, outcome, and intended decision. A method successful for one formulation family may fail when excipient interactions, solid state, rheology, stability, dose, release mechanism, or physiology changes. This heterogeneity made quantitative aggregation and universal ranking inappropriate. JBI-informed charting supports mapping such variation but cannot convert unlike evidence into direct comparability [2].

Reporting completeness and publication patterns may also distort the map. Publication bias may favour successful formulations, positive models, novel devices, or integrated demonstrations. Failed scale-up, unstable products, weak transfer, impractical workflows, and abandoned technologies may be underreported.

Finally, the qualitative maturity framework is not an evidence grade or readiness score. Machine-learning performance remains dependent on dataset and domain [12]; PBBM credibility remains context-specific [16]; and translation evidence for printed pharmaceuticals remains uneven [29]. Feasibility, verification, validation, translation, and implementation may proceed iteratively or in parallel. The framework should identify missing links and clarify claims, not make clinical, regulatory, procurement, or investment decisions without product-specific evaluation.

## CONCLUSION

Advanced pharmaceutical formulations are cross-scale systems in which digital models, materials, dosage-form design, manufacturing operations, analytical control, biopharmaceutic behaviour, and patient use contribute different but interdependent evidence. The literature shows substantial technical activity, yet evidence strength remains uneven across validation and translation layers. Computational accuracy cannot substitute for pharmaceutical utility; laboratory feasibility cannot substitute for manufacturing robustness; analytical similarity cannot substitute for clinical equivalence; and acceptability cannot substitute for adherence or therapeutic benefit. This scoping review provides an evidence-bounded taxonomy and integration framework that makes those distinctions explicit. The framework also clarifies that stability, manufacturability, bioavailability, and usability are connected but non-equivalent development concerns. Their relationships should be examined through product-specific evidence, because success at one interface cannot reliably compensate for an unresolved material, process, analytical, biological, or human-factors limitation elsewhere in the pathway. Progress depends less on novelty alone than on transparent data, fit-for-purpose validation, reproducible manufacture, population-aware formulation decisions, and credible links between product attributes and real-world use.

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