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DIGITAL PHARMACEUTICS: ARTIFICIAL INTELLIGENCE, 3D PRINTING, AND SMART MANUFACTURING IN PHARMACY

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ABSTRACT

Digital technologies are increasingly being incorporated into pharmaceutical formulation and manufacturing to improve process understanding, flexibility, and patient-centred product design. This narrative review examines the scientific basis, pharmaceutical applications, quality considerations, and regulatory landscape of artificial intelligence (AI)/machine learning (ML), three-dimensional (3D) printing, and smart or continuous manufacturing. Literature was identified from PubMed, ScienceDirect, SpringerLink, MDPI journals, and official FDA and ICH sources, with emphasis on publications from 2018 to 2026 and inclusion of earlier landmark studies. Evidence was organized narratively by technology, formulation and process-development considerations, pharmaceutical applications, quality assurance, regulation, and translational barriers. The reviewed literature shows that AI/ML can support formulation optimization, predictive modelling, and process monitoring, but model performance remains dependent on representative data, external validation, and appropriate human oversight. 3D printing enables individualized dose strengths, complex release profiles, and multidrug dosage forms; however, excipient limitations, reproducibility, throughput, stability, and regulatory validation remain important barriers. Smart and continuous manufacturing can integrate process analytical technology (PAT), automation, and data analytics to strengthen process control and facilitate real-time quality assessment,

with continuous manufacturing supported by ICH Q13. Regulatory development for AI remains comparatively less mature: FDA materials include discussion papers, 2025 draft guidance, and 2026 non-binding guiding principles. Overall, the technologies are complementary rather than interchangeable, and their wider clinical and industrial adoption will depend on robust validation, scalable manufacturing platforms, workforce capability, data governance, and regulatory clarity.

KEYWORDS: Artificial Intelligence; Machine Learning; Three-Dimensional Printing; Continuous Manufacturing; Process Analytical Technology; Personalized Dosage Forms.

1. INTRODUCTION

Conventional pharmaceutical manufacturing has traditionally relied on discrete batch operations, predetermined dosage strengths, sequential unit operations, and extensive finished-product testing. These systems are highly established and remain the basis of large-scale medicine production, but they can be less flexible for products requiring rapid development, frequent process adjustment, or individualized dosing. Pharmaceutical formulation development also commonly requires iterative laboratory experimentation because relationships among active pharmaceutical ingredients (APIs), excipients, process variables, and product performance are complex. Machine-learning approaches have been proposed to reduce this burden by learning relationships from experimental datasets and prioritizing promising formulations for laboratory verification.[1-4]

Research has demonstrated personalized tablets, multidrug polypills, and modified-release structures, while the FDA approval of Spritam (levetiracetam) established a regulatory precedent for a 3D-printed drug product.[9-14,24]. Smart manufacturing extends digitalization into process execution. Process analytical technology (PAT), continuous manufacturing, automation, data analytics, and digital-twin approaches can provide more timely information about process state and product quality than periodic sampling alone. FDA's PAT framework and ICH Q13 provide established regulatory and scientific foundations for process monitoring and continuous manufacturing, while more recent work is exploring AI-enabled control and self-optimization.[17-20]

The central problem is therefore not whether any single digital technology can replace conventional pharmaceutics, but how computational modelling, additive manufacturing, and data-rich process control can be integrated without compromising pharmaceutical quality, safety, reproducibility, or regulatory compliance. Evidence is also uneven: some applications

have progressed into regulated manufacturing, whereas others remain predominantly in silico or laboratory-scale. An integrated narrative review is useful because the technologies interact across formulation development, manufacturing, quality assurance, regulatory science, and future pharmacy practice. This review therefore synthesizes the scientific principles, applications, representative studies, quality considerations, regulatory developments, limitations, and realistic future opportunities for AI/ML, 3D printing, and smart manufacturing in pharmacy.[1-20]

2. MATERIAL AND METHODS

Study design. This work was conducted as a narrative literature review. It was not designed or reported as a systematic review, meta-analysis, or scoping review, and no PRISMA protocol or formal quantitative synthesis was used. The objective was to identify representative and authoritative literature that explains the scientific basis, pharmaceutical applications, quality implications, and regulatory context of digital pharmaceutics.

Information sources. Literature was identified from PubMed, ScienceDirect, SpringerLink, and MDPI journals, including Pharmaceutics, together with official regulatory and standards sources from the U.S. Food and Drug Administration (FDA) and International Council for Harmonisation (ICH). Reference lists of relevant review articles were examined to identify landmark primary studies and additional authoritative sources. General web searches were used only to locate or cross-check official regulatory material; non-peer-reviewed promotional material was not used as scientific evidence.

Search concepts. Search terms were used individually and in combinations related to the principal themes of the review, including: artificial intelligence pharmaceutics; machine learning drug formulation; AI pharmaceutical technology; 3D printing drug delivery; pharmaceutical additive manufacturing; personalized dosage forms; polypill 3D printing; continuous manufacturing; process analytical technology; Pharma 4.0; digital twin; and quality by design.

Literature period and source selection. The search emphasis was 2018-2026, while earlier landmark studies were retained when they were important for understanding the development of 3D-printed medicines or AI-enabled formulation science. Priority was given to peer-reviewed original research, high-quality narrative or systematic reviews, and official regulatory documents. Sources were considered relevant when they addressed at least one of the review themes and contained sufficient methodological or regulatory detail to support a statement made in the manuscript. Studies were excluded from substantive synthesis when

they were duplicative, purely promotional, unrelated to pharmaceutical applications, or insufficiently documented for reliable citation.

Selection and synthesis. The identified literature was selected qualitatively according to relevance to the review questions rather than by a formal risk-of-bias workflow. Findings were organized into technology-specific themes and then compared across formulation, manufacturing, quality, regulatory, and pharmacy-practice dimensions. Representative studies were selected to illustrate distinct stages of translation, including computational formulation modelling, 3D-printed dosage-form development, continuous manufacturing, and current regulatory initiatives. Regulatory statements were checked against official FDA or ICH sources and were classified as final guidance/guideline, discussion paper, draft guidance, or non-binding initiative where appropriate.

Methodological limitation. Because this was a narrative review, the search was not designed to be exhaustive and publication selection involved qualitative judgement. The review may therefore underrepresent unpublished, negative, or less readily indexed evidence. No pooled effect estimates or statistical claims of comparative superiority were generated.

3. Scientific Background

3.1 Artificial Intelligence, Machine Learning, and Deep Learning

Artificial intelligence (AI) describes computational systems capable of making predictions, recommendations, or decisions from data-defined inputs, while machine learning (ML) refers to methods that learn patterns or relationships from data. In pharmaceutical science, supervised models such as artificial neural networks (ANNs), random forests, and support vector machines can be used to predict formulation or process outcomes. Deep learning uses multi-layer neural networks and can be useful when the input data are high-dimensional, including images or spectroscopic signals. Generative models extend prediction by producing candidate structures or formulation representations that can then be evaluated experimentally [1-4]

3.2 Additive Manufacturing (3D Printing)

3D printing is an additive manufacturing process in which material is deposited, bound, or solidified according to a digital design. In pharmaceutics, the digital design can encode tablet geometry, internal structure, infill density, layer arrangement, or multiple drug-containing regions. These variables create opportunities to alter dose, shape, porosity, and drug-release behaviour while avoiding some constraints of conventional compression [9-14]

3.3 Smart Manufacturing, Pharma 4.0, and Continuous Manufacturing

Smart manufacturing combines connected equipment, sensors, data acquisition, analytics, automation, and process control. In pharmaceutical applications, these elements are often discussed under the broader concept of Pharma 4.0. Continuous manufacturing (CM) involves continuous feeding of input materials, integrated processing through two or more connected unit operations, and concomitant removal of output material. PAT supplies timely process measurements, while advanced control, data analytics, and digital-twin models can support process understanding and response to deviations.[17-20]

3.4 Quality by Design and Critical Quality Attributes

Quality by Design (QbD) is a development approach that begins with predefined objectives and uses scientific and risk-based understanding of materials, process variables, and product performance. A Critical Quality Attribute (CQA) is a physical, chemical, biological, or microbiological property that should remain within an appropriate range to ensure product quality; a Critical Process Parameter (CPP) is a process variable whose variability can affect a CQA. QbD therefore provides a useful framework for linking AI models, formulation experiments, PAT measurements, and process-control strategies.[5,6,17]

4. Technologies and Classification

The major technologies relevant to pharmaceutical digitalisation can be grouped into AI/ML methods, additive-manufacturing methods, and smart/continuous manufacturing components. Their principles, uses, and main constraints are summarized in Table 2.

Table 1. Comparison of conventional and digital/smart pharmaceutical technology.

Feature	Conventional approach	Digital/smart approach
Manufacturing mode	Discrete batch processing	Continuous or highly connected processing with integrated unit operations
Quality approach	Periodic and end-point testing	In-process monitoring supported by PAT and data analytics
Dose flexibility	Predetermined strengths	Potential for individualized strengths and complex dosage forms
Formulation development	Iterative experimental screening	Predictive modelling and data-driven prioritization with laboratory confirmation
Process control	Manual or periodic adjustment	Sensor-based monitoring and model-supported control
Data environment	Relatively fragmented batch records	Integrated digital data streams and model-based analytics

Table 2. Major AI/ML, 3D-printing, and smart-manufacturing technologies.

Domain	Technology	Principle	Representative pharmaceutical use	Key limitation
AI/ML	Artificial neural networks	Learn nonlinear relationships from labelled data	Prediction of formulation/process performance [5,6]	Dependence on data quality and external validation
AI/ML	Generative models	Generate candidate structures or formulations from learned data distributions	In-silico formulation and product-structure exploration [1,7]	Outputs require experimental confirmation
AI/ML	Reinforcement/self-optimizing algorithms	Update control actions according to a defined objective or reward	Adaptive process optimization in research settings [18]	Requires validated control boundaries and reliable models
3D printing	Fused deposition modelling (FDM)	Thermoplastic filament is melted and extruded layer-by-layer	Personalised tablets and polypills [10-13]	Thermal stress and material limitations
3D printing	Binder jetting	Binder is selectively deposited onto powder layers	Highly porous, rapidly disintegrating tablets such as Spritam [11,14]	Mechanical strength and process control considerations
3D printing	Stereolithography/digital light processing	Light cures a photopolymerizable formulation layer-by-layer	Complex, high-resolution dosage-form geometries [13,15]	Photopolymer/residual-monomer and safety considerations
3D printing	Semi-solid extrusion	Paste or gel is deposited through a nozzle	Heat-sensitive and paediatric formulations [10,13]	Rheology, throughput, and mechanical-strength constraints
Smart manufacturing	PAT	Timely in-process measurements and multivariate analysis	Monitoring and control of process state and product quality [17]	Instrument, chemometric, and validation burden
Smart manufactur	Continuous manufacturing	Integrated continuous	Consistent and flexible	Capital, integration, and

ing		feed, processing, and withdrawal	production with lifecycle control [19,20]	operational expertise
Smart manufacturing	Digital twin	Data-driven virtual representation of a physical process	Simulation, prediction, and process understanding [18]	Model fidelity depends on data and process knowledge

5. Formulation and Development Considerations

5.1 Drug and Excipient Selection

AI-assisted formulation development is most useful when sufficient, consistent, and relevant historical data are available. Model inputs may include API physicochemical properties, excipient descriptors, formulation composition, process variables, and measured CQAs. The resulting predictions remain decision-support tools rather than substitutes for formulation experiments and pharmaceutical development judgement.[1-4,6]

For 3D printing, material choice is strongly linked to the printing mechanism. FDM generally requires thermoplastic polymers that can be processed at the selected temperature; the potential for thermal degradation therefore needs early evaluation. Semi-solid extrusion is governed by paste rheology, extrudability, and shape retention. Photopolymer-based approaches require careful assessment of the photochemical environment and formulation components. Across all methods, excipient suitability must be considered together with drug loading, mechanical performance, stability, and release behaviour [9,10,13,15].

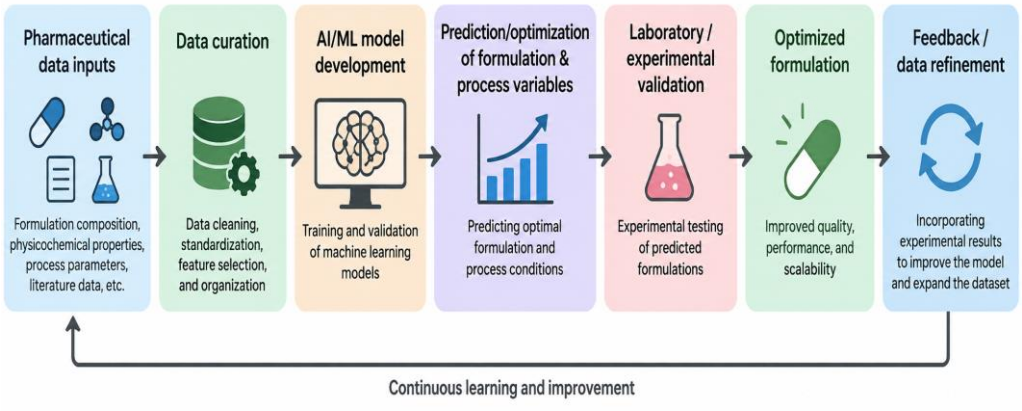


Figure 1. Schematic representation of the use of pharmaceutical formulation and process data for model development, prediction of critical product attributes, formulation/process optimisation, experimental validation, and iterative refinement within a quality-by-design framework.

5.2 Formulation and Process Variables

Important variables for printed dosage forms include drug loading, polymer type and concentration, plasticizer content, nozzle or processing temperature, printing speed, layer height, infill density, and geometry. Changes in porosity and internal structure can alter mechanical strength and drug release. In continuous manufacturing, feed rate, residence time, blending conditions, granulation or drying parameters, and control strategy can influence downstream product quality [10,12,13,19,20]

5.3 Physicochemical Stability

Thermal, photochemical, and moisture-related degradation risks must be assessed early, particularly when FDM or photopolymerisation is used. The reported 4-ASA/FDM study illustrates why thermal analysis can be important: substantial thermal degradation occurred for 4-ASA under the printing conditions, while 5-ASA was successfully printed. These findings support technology-specific preformulation rather than assuming that all APIs are suitable for every printing process.[12]

5.4 Dosage-Form Design and Release

The digital nature of 3D printing permits dosage-form geometry to become a design variable. Surface area, internal channels, infill density, and multi-compartment arrangements can be selected to influence disintegration or drug-release behaviour. Such design freedom expands the formulation space but also increases the need for robust process control, characterization, and validated relationships between design inputs and CQAs. [12-16]

6. Pharmaceutical Applications

6.1 AI in Formulation Development and Product Design

ML-directed formulation development can reduce the number of experimental candidates that require direct testing by learning relationships between materials, process variables, and measured outcomes. Reviews describe applications in formulation screening, predictive dissolution or product performance, and advanced modelling workflows, while the literature also highlights the importance of dataset representativeness, validation, uncertainty, and reporting quality [1-4,6]

A representative original study integrated AI with QbD to develop lecithin/chitosan nanoparticles containing silymarin. The authors combined experimental design with ANN models to predict drug release and used the model to support optimization of the formulation and process space. The study illustrates a useful pattern for pharmaceutical AI: computation

is most informative when it is connected to experimental design and laboratory validation rather than used as a standalone source of evidence.[6]

6.2 AI in Quality Control and Process Monitoring

AI/ML methods can be combined with PAT and other process data to detect trends, classify process states, and support prediction of quality-related outcomes. In this setting, the model complements rather than replaces the analytical measurement system.

The FDA discussion paper on AI in drug manufacturing specifically considers AI-enabled manufacturing applications within the existing regulatory framework and emphasizes questions around model performance, data, lifecycle management, and regulatory oversight.[17,21]

6.3 3D Printing for Personalized Dosage Forms and Polypills

3D printing enables individualized dosage strength and complex dosage-form architecture and has therefore become an important research platform for personalized oral medicines. Studies have demonstrated modified-release tablets, paediatric dosage forms, and polypills containing multiple active ingredients or distinct compartments.

Recent reviews indicate substantial research activity but also emphasize persistent translational barriers involving reproducibility, production scale, material selection, stability, and regulation.[9-16]

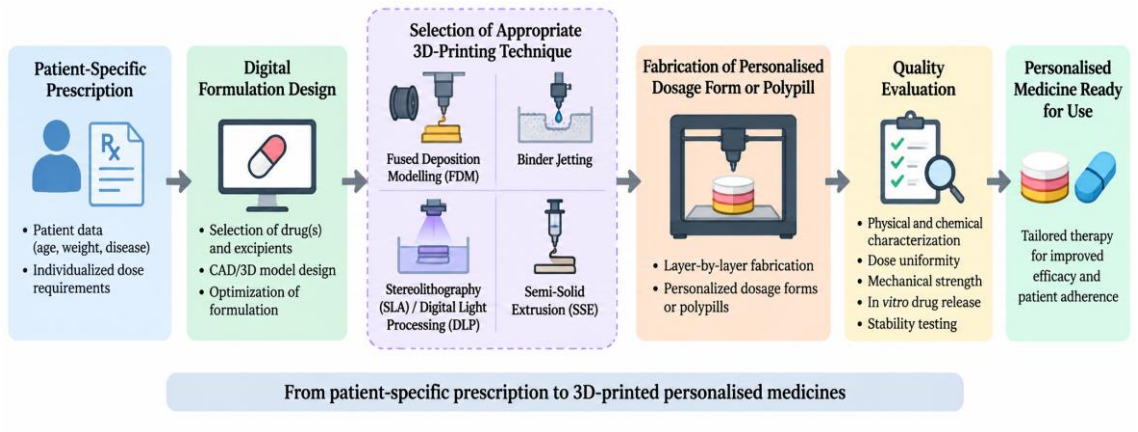


Figure 2. Conceptual workflow from patient-specific prescription and digital formulation design to selection of an appropriate additive-manufacturing technique, fabrication of personalised dosage forms or polypills, and subsequent quality evaluation. Major pharmaceutical 3D-printing approaches include fused deposition modelling, binder jetting, stereolithography/digital light processing, and semi-solid extrusion.

6.4 3D Printing Beyond Conventional Oral Dosage Forms

Additive manufacturing has also been investigated for implants, medical devices, and research models such as organ-on-chip or tissue-engineering constructs. These applications broaden the pharmaceutical relevance of 3D printing but remain heterogeneous and, in many cases, research-oriented rather than routine clinical manufacturing. Their translational requirements differ from those of conventional oral tablets and therefore should not be treated as a single regulatory or manufacturing category [14]

Additive manufacturing has also been investigated for implants, medical devices, and research models such as organ-on-chip or tissue-engineering constructs, significantly broadening the overall pharmaceutical relevance and clinical potential of 3D printing technology. However, current developments remain highly heterogeneous and are mostly restricted to specialized, research-oriented exploratory work rather than achieving widespread adoption in routine clinical manufacturing processes. Because the translational, quality, and material requirements for these complex bioprinted constructs differ fundamentally from traditional solid dosage forms, manufacturing standards cannot be directly mapped onto conventional oral tablets. Consequently, regulators must establish distinct evaluation frameworks rather than treating all 3D-printed healthcare products as a single regulatory category, ensuring that future safety protocols and approval pathways are properly tailored to each specific medical application[15]

6.5 Smart and Continuous Manufacturing

Continuous manufacturing can integrate several unit operations and provide a more data-rich manufacturing environment than disconnected batch steps. PAT measurements can be used to estimate process and product attributes during production, while residence-time and diversion strategies can help manage non-conforming material. ICH Q13 establishes scientific and regulatory considerations for the development, implementation, operation, and lifecycle management of continuous manufacturing of drug substances and drug products. [17,19,20]

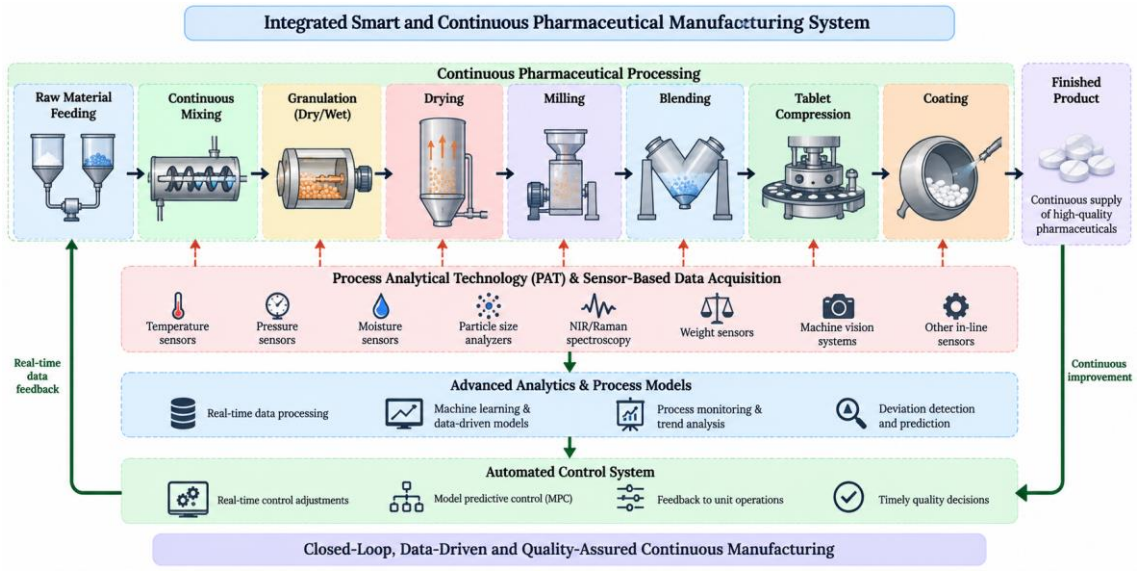


Figure 3. Schematic representation of continuous pharmaceutical processing supported by process analytical technology, sensor-based data acquisition, advanced analytics, and automated control. In-process measurements can be integrated with process models and data-driven tools to support process monitoring, control, deviation detection, and timely quality decisions across interconnected manufacturing operations.

6.6 AI-Supported Pharmacy Practice

Beyond product development and manufacturing, AI is being evaluated in pharmacy practice for workflow support, medication-related decision support, prescription screening, and other service functions. Recent reviews suggest that current implementations are more concentrated on workflow and information-processing tasks than on demonstrated improvements in patient outcomes. These findings support a cautious interpretation of AI in pharmacy practice: the technology is an adjunct to professional judgement, not a substitute for pharmacist oversight [22,23].

7. RESULT AND DISCUSSION

Four broad observations were consistently supported: AI/ML is most useful when integrated with high-quality formulation or process datasets and experimental validation; 3D printing provides the strongest current evidence for flexible oral dosage-form design and personalization; continuous manufacturing has the clearest harmonized regulatory framework among the three technology areas; and the principal barriers to wider implementation are validation, reproducibility, data governance, scale, cost, and regulatory translation.[1-23,25,26]

7.1 Comparative Maturity of the Technologies

The literature does not support ranking the three technologies by a single measure of 'maturity.' Continuous manufacturing is relatively mature from a regulatory and industrial perspective because ICH Q13 explicitly addresses its development and lifecycle management, and PAT has a long-standing FDA framework.[17,19,20] 3D printing has a strong proof-of-concept base and a clear FDA-approved precedent in Spritam, but the number of marketed products remains very small relative to the research literature.[11,14,24] AI/ML has broad application across formulation and process-development research and is increasingly encountered in regulatory submissions, but regulatory expectations for AI models remain an evolving area, particularly when model use affects regulatory decision-making or manufacturing controls.[1-4,21,25,26]

7.2 Evidence Strength and Translation Gaps

Evidence is strongest when an AI model is trained on experimentally generated pharmaceutical data and tested on appropriately separated validation data, or when a 3D-printing method is linked to measurable product performance and stability. By contrast, many generative-AI and autonomous-control concepts remain computational or laboratory-stage technologies. The 2024 generative-AI study by Hornick and colleagues demonstrated digital generation and optimization of pharmaceutical product structures, but the work still depends on the translation of computational outputs into controlled physical manufacturing.[7] Similar translation gaps are visible in personalized polypill research, where technical demonstrations exceed the level of regulatory and industrial standardization currently available.[15,16]

7.3 Complementarity of Digital Technologies

The main practical insight from the literature is that these technologies can form a connected development-and-manufacturing chain. AI can help prioritize formulations or predict process behaviour; 3D printing can convert a digital prescription into a customized dosage form; and PAT, continuous manufacturing, and data analytics can provide in-process control and traceability. Such integration is conceptually attractive, but each link introduces its own validation burden. A reliable digital pipeline therefore requires control of data quality, model performance, printer/process capability, material variability, analytical procedures, and change management [17-20]

7.4 Implications for Pharmaceutical Science and Pharmacy

For pharmaceutical scientists, the shift toward digital pharmaceutics strengthens the importance of multidisciplinary skills spanning pharmaceutics, statistics, data science, analytical technology, process engineering, and regulatory science.

For pharmacists, the immediate implication is not replacement of dispensing or professional decision-making, but a growing need to understand the provenance and limitations of digitally generated information and, potentially, the quality requirements of patient-specific manufacturing. Pharmacy-level or point-of-care manufacturing remains an emerging proposition that would require validated equipment, controlled materials, documented procedures, trained personnel, and appropriate regulatory oversight [22,23].

Table 3. Representative studies and regulatory milestones.

Year	Reference	Type	Technology or topic	Key contribution
2015	[12]	Original research	FDM 3D printing of 4-ASA/5-ASA tablets	Demonstrated geometry/infill-dependent release and identified drug-specific thermal limitations.
2015	[24]	Regulatory precedent	Binder-jet 3D printing (ZipDose)	Established an FDA-approved 3D-printed levetiracetam tablet product.
2020	[5]	Original research	ANN within QbD	Linked material/process variables to product performance and demonstrated industrial and clinical development relevance.
2023	[6]	Original research	AI + QbD nanoparticles	Integrated experimental design and ANN prediction for formulation optimization and release prediction.
2024	[7]	Original research	Generative AI / digital product structures	Demonstrated in-silico generation and analysis of pharmaceutical product structures for formulation and particle engineering.
2024	[18]	Review	PAT and self-optimization	Summarized advanced PAT and self-optimization strategies for automated continuous pharmaceutical

				manufacturing.
2025	[20]	Review	Continuous manufacturing and digitalization	Reviewed recent digitalization trends and continuous-manufacturing implementation considerations.
2025	[15]	Review	3D printing and personalized medicine	Synthesized emerging applications across personalized dosage forms, polypills, bioprinting, and decentralized manufacturing.
2025/2026	[16]	Review	3D-printed polypills	Highlighted the personalization potential and translational barriers for polypills.
2026	[21,24]	Regulatory materials	AI in drug development/manufacturing	Shows an evolving framework comprising discussion papers, draft guidance, and non-binding guiding principles.

8. Quality Control and Quality Assurance

Digital manufacturing does not reduce the need for pharmaceutical quality; rather, it changes where and how quality information is generated. Regardless of platform, product specifications and appropriate compendial or regulatory requirements remain applicable, while technology-specific controls are required for new materials, equipment, software, and manufacturing workflows.[13,17,19,20]

8.1 Assay and Content Uniformity

Dose accuracy is especially important for personalized or multi-drug printed dosage forms because differences among individual units may be intentional but must remain within predefined specifications. PAT or other suitable in-process measurements may provide additional assurance when sampling every unit is impractical, but the analytical strategy requires demonstrated performance and an appropriate link to product quality[13,17]

8.2 Dissolution and Drug Release

Complex internal geometries, porous structures, and multi-compartment designs can produce release behaviour that differs from conventional compressed tablets. Dissolution procedures

may therefore require careful method selection, development, or justification for the particular dosage form. Conventional release testing remains important even when digital design is used to control the release mechanism.[12-14]

8.3 Mechanical Properties and Stability

Hardness, friability, tensile or mechanical strength, dimensional accuracy, and structural integrity may be critical for printed oral dosage forms. Stability programmes must address API degradation, drug-polymer interactions, moisture sensitivity, physical changes, and, for photopolymer systems, residual components relevant to product safety. The specific tests required depend on the dosage form and material system[10,13,14]

8.4 Process Validation, CPV, Equipment, and Software

For AI/ML systems, validation should address the defined context of use, data provenance, model performance, change control, and continued suitability rather than relying solely on generic software testing.[4,21,25,26]

8.5 Data Integrity

Digital pharmaceutics increases the volume and importance of electronic records, model inputs, instrument data, and automated decisions. Data-integrity controls should therefore ensure that records are attributable, legible, contemporaneous, original or true copies, accurate, complete, consistent, enduring, and available. Particular attention is required when model outputs influence manufacturing or quality decisions [20,21]

9. Regulatory Perspective

9.1 3D Printing

The FDA approval of Spritam in 2015 is a clear regulatory precedent demonstrating that a 3D-printed drug product can be evaluated within an established pharmaceutical approval pathway. The FDA approval and quality-review documents identify Spritam as a novel, highly porous levetiracetam tablet manufactured using a 3D-printing approach.[11,14,24] Importantly, this precedent does not create a separate universal 3D-printing approval pathway; future products remain subject to product-specific quality, safety, efficacy, manufacturing, and controls requirements.

9.2 Continuous Manufacturing and PAT

ICH Q13 is a finalized harmonized guideline addressing scientific and regulatory considerations for the development, implementation, operation, and lifecycle management of continuous manufacturing of drug substances and drug products. FDA's PAT framework is

also a finalized guidance intended to encourage innovative pharmaceutical development, manufacturing, and quality assurance.

These instruments make continuous manufacturing and PAT comparatively more established from a regulatory-science perspective than many newer digital technologies.[17,19,20]

9.3 Artificial Intelligence in Drug Development and Manufacturing

FDA's current AI materials show that regulation is evolving rather than absent. FDA published discussion papers on AI in drug manufacturing and AI/ML in drug development in 2023; the agency subsequently published the 2025 draft guidance "Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products." The 2025 document is explicitly identified by FDA as draft, non-binding, and not for implementation. FDA's current drug-development AI webpage also lists.

"Guiding Principles of Good AI Practice in Drug Development" published in January 2026, alongside the 2025 draft guidance and 2023 discussion papers. These guiding principles represent regulatory direction and good-practice expectations, but they should not be described as equivalent to a binding AI-specific rule.[21,25,26]

9.4 Regulatory Interpretation for Reviewers and Applicants

The regulatory status of digital technologies should therefore be described precisely. ICH Q13 is a harmonized guideline for continuous manufacturing; FDA's PAT framework is a final guidance; FDA discussion papers are consultation and policy-development documents; and the 2025 AI draft guidance is non-binding until finalized. This distinction is essential when describing the current maturity of digital-pharmaceutics regulation [17,19,21,25,26]

10. Benefits and Limitations

10.1 Artificial Intelligence/Machine Learning

- Potential benefits: faster hypothesis generation; data-driven formulation prioritization; predictive modelling of product attributes; support for process monitoring; and structured analysis of large datasets.[1-4]
- Key limitations: dependence on high-quality representative data; risk of overfitting or poor external generalization; limited interpretability for some models; model drift or uncontrolled changes; and the need for experimental and regulatory validation.[4,6,21,25,26]

10.2 3D Printing

- Potential benefits: individualized dose and geometry; polypill fabrication; complex release profiles; digital design-to-product workflows; and potential for decentralized or point-of-care manufacturing.[9-16]

- Key limitations: restricted excipient/material options; process-dependent drug degradation; mechanical-strength challenges; printer-to-printer variability; limited throughput relative to conventional high-speed tableting; stability uncertainty; and unresolved scale-up and regulatory questions.[10,13,15,16]

10.3 Smart/Continuous Manufacturing

- Potential benefits: integrated processing; data-rich process understanding; faster detection of deviations; reduced dependence on delayed testing; and improved process-control opportunities.[17-20]
- Key limitations: capital and integration costs; complex validation and data architecture; need for specialized personnel; dependence on sensor/model reliability; and evolving implementation practices for advanced control strategies [17-20]

Table 4. Technology-specific benefits and limitations.

Domain	Principal opportunities	Principal limitations
AI/ML	Predictive formulation and process analytics; faster candidate prioritization	Data quality, model validation, explainability, lifecycle management
3D printing	Personalised dosage forms; complex geometries; polypills; on-demand design	Material limitations, reproducibility, throughput, stability, scale-up
Smart/continuous manufacturing	Real-time process understanding; integrated control; lifecycle monitoring	Capital/integration burden, validation complexity, workforce requirements

11. Future Perspectives

11.1 Near-Term Opportunities

The most realistic near-term opportunities are incremental rather than fully autonomous. These include broader use of validated PAT systems; greater adoption of continuous manufacturing where the process is technically and economically suitable; improved datasets and reporting standards for ML-assisted formulation development; and carefully controlled pilot studies of patient-specific 3D printing in hospital or pharmacy environments.

FDA's continuing advanced-manufacturing initiatives and AI publications indicate ongoing regulatory engagement, but adoption will depend on product-specific evidence and appropriate oversight.[,20,21]

11.2 Longer-Term Possibilities

Longer-term possibilities include validated pharmacy-level dose printing, multi-drug dosage forms generated directly from electronic prescriptions, digital twins linked to manufacturing

control, and more autonomous optimization within predefined validated operating boundaries. These scenarios remain conditional on evidence demonstrating safety, reproducibility, cybersecurity, data integrity, cost-effectiveness, and regulatory acceptability; they should not be presented as routine practice today.[15,16,18,20]

Table 5. Future opportunities and evidence gaps.

Area	Realistic opportunity	Major evidence or implementation gap
AI in formulation	Validated predictive models integrated with QbD and experiment planning	Prospective external validation and robust lifecycle/change-control frameworks
3D-printed dosage forms	Patient-specific strengths and selected polypill applications	Scale-up, reproducibility, stability, GMP implementation, and regulatory standardization
Smart manufacturing	Expanded PAT/continuous manufacturing and model-supported control	Long-term operational evidence and validated advanced-control strategies
Pharmacy practice	Decision support and workflow augmentation	Evidence of patient-outcome benefit, training, governance, and accountability
Regulatory science	Convergent principles for credible AI use and advanced manufacturing	Harmonization and clarification of model lifecycle, validation, and implementation expectations

12. CONCLUSION

Digital pharmaceutics is emerging as an important transformation in pharmaceutical science, bringing together artificial intelligence and machine learning, three-dimensional printing, process analytical technology, automation, continuous manufacturing, and data-driven quality management. The present review demonstrates that these technologies are not isolated innovations but interconnected components of a broader pharmaceutical development and manufacturing ecosystem. Their value lies in improving the way medicines are designed, produced, monitored, and adapted to individual patient requirements. However, their successful implementation cannot be judged solely by technological novelty. In pharmaceutical practice, every innovation must ultimately be evaluated according to its ability to produce medicines that are safe, effective, reproducible, stable, accessible, and compliant with regulatory and quality standards.

Artificial intelligence and machine learning have shown considerable potential in formulation development and pharmaceutical process optimization. Traditional formulation development often involves extensive laboratory experimentation because the relationships among drug properties, excipient characteristics, processing conditions, and product performance are

complex and frequently nonlinear. AI/ML models can assist researchers by identifying patterns within formulation and process datasets, predicting critical quality attributes, prioritizing experimental combinations, and reducing unnecessary trial-and-error studies. Their greatest contribution is therefore not the complete replacement of experimental pharmaceutics, but the intelligent selection of experiments that are more likely to produce useful outcomes. When integrated with Quality by Design principles, design of experiments, mechanistic understanding, and laboratory confirmation, AI can support a more rational and efficient approach to pharmaceutical development.

Nevertheless, AI-based prediction should not be confused with pharmaceutical evidence. A model may produce highly accurate results within the dataset used for its development but perform poorly when applied to a different formulation, manufacturing platform, equipment configuration, or patient population. This limitation is particularly important in pharmaceutical science, where small differences in raw-material properties, environmental conditions, equipment geometry, or processing history can influence final product quality. Consequently, AI/ML models must be developed using representative and well-curated data, appropriately separated training and validation datasets, predefined performance criteria, uncertainty assessment, and external verification. Model interpretability, version control, change management, data provenance, and continued performance monitoring are also essential. The final scientific decision must remain connected to formulation knowledge, analytical evidence, and professional judgement rather than being based exclusively on an algorithmic output.

The integration of AI with Quality by Design represents one of the most scientifically meaningful opportunities identified in this review. QbD establishes a structured relationship between the quality target product profile, critical quality attributes, critical material attributes, critical process parameters, risk assessment, and the design space. AI can strengthen this framework by analysing multidimensional relationships that may be difficult to identify using conventional statistical approaches alone. For example, neural-network models have been used to associate formulation and process variables with drug release and other performance characteristics. Such applications show that AI is most valuable when it is embedded within a scientifically defined development strategy. The model should answer a clearly stated pharmaceutical question, operate within a defined context of use, and be supported by experiments that confirm whether the predicted relationship is meaningful in the physical product.

Three-dimensional printing provides a different but complementary contribution to digital pharmaceutics. Unlike AI, which primarily enhances prediction and decision-making, 3D printing directly changes the way a dosage form can be designed and manufactured. It enables the digital control of tablet shape, internal architecture, infill density, porosity, layer arrangement, and drug-containing compartments. These features can be used to develop dosage forms with individualized strengths, complex release patterns, multiple active pharmaceutical ingredients, and patient-specific geometries. Such capabilities are particularly relevant to paediatric, geriatric, polypharmacy, and precision-medicine applications, in which conventional fixed-strength dosage forms may not adequately address individual therapeutic needs.

Process analytical technology is central to this transformation. PAT allows important process or product characteristics to be measured during manufacturing rather than being assessed only after production is complete. When combined with chemometrics, multivariate analysis, residence-time modelling, and automated control, PAT can support timely decisions regarding process state and material quality. This does not eliminate the need for conventional finished-product testing, but it can add a more comprehensive layer of process knowledge. It can also support continued process verification by identifying trends that may not be visible through occasional sampling. In this manner, quality becomes increasingly built into the process rather than being assessed only at the end.

In conclusion, AI/ML, 3D printing, and smart/continuous manufacturing have the potential to reshape pharmaceutical formulation, manufacturing, quality assurance, and patient-centred care. AI can make development more predictive, 3D printing can make dosage forms more adaptable, and smart manufacturing can make production more connected and responsive. Yet the true success of digital pharmaceutics will not be measured by the sophistication of its algorithms, the novelty of its printers, or the extent of automation. It will be measured by whether these technologies consistently produce high-quality medicines and meaningfully improve patient care. The most responsible future is one in which digital innovation is combined with mechanistic understanding, experimental evidence, robust quality systems, regulatory transparency, and continuous professional oversight. Under these conditions, digital pharmaceutics can progress from an emerging technological concept to a scientifically credible, clinically relevant, and ethically responsible foundation for the next generation of pharmaceutical practice.

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REFERENCES

1. Bannigan P, Aldeghi M, Bao Z, Häse F, Aspuru-Guzik A, Allen C. Machine learning directed drug formulation development. Adv Drug Deliv Rev. 2021;175:113806. doi:10.1016/j.addr.2021.05.016.
2. Carracedo-Reboredo P, Liñares-Blanco J, Rodríguez-Fernández N, Cedrón F, Novoa FJ, Carballal A, et al. A review on machine learning approaches and trends in drug discovery. Comput Struct Biotechnol J. 2021;19:4538-4558. doi:10.1016/j.csbj.2021.08.011.
3. Vora LK, Gholap AD, Jetha K, Thakur RRS, Solanki HK, Chavda VP. Artificial intelligence in pharmaceutical technology and drug delivery design. Pharmaceutics. 2023;15(7):1916. doi:10.3390/pharmaceutics15071916.
4. Murray JD, Lange JJ, Bennett-Lenane H, Holm R, Kuentz M, O'Dwyer PJ, et al. Advancing algorithmic drug product development: recommendations for machine learning approaches in drug formulation. Eur J Pharm Sci. 2023;191:106562. doi:10.1016/j.ejps.2023.106562.
5. Simões MF, Silva G, Pinto AC, Fonseca M, Silva NE, Pinto RMA, et al. Artificial neural networks applied to quality-by-design: from formulation development to clinical outcome. Eur J Pharm Biopharm. 2020;152:282-295. doi:10.1016/j.ejpb.2020.05.012.
6. Dawoud MHS, Mannaa IS, Abdel-Daim A, Sweed NM. Integrating artificial intelligence with quality by design in the formulation of lecithin/chitosan nanoparticles of a poorly water-soluble drug. AAPS PharmSciTech. 2023;24(6):169. doi:10.1208/s12249-023-02609-5.
7. Hornick T, Mao C, Koynov A, Yawman P, Thool P, Salish K, et al. In silico formulation optimization and particle engineering of pharmaceutical products using a generative artificial intelligence structure synthesis method. Nat Commun. 2024;15(1):9622. doi:10.1038/s41467-024-54011-9.

8. Cunha S, Pina Costa C, Moreira JN, Sousa Lobo JM, Silva AC. Using the quality by design (QbD) approach to optimize formulations of lipid nanoparticles and nanoemulsions: a review. Nanomedicine. 2020;28:102206. doi:10.1016/j.nano.2020.102206.
9. Warsi MH, Yusuf M, Al Robaian M, Khan M, Muheem A, Khan S. 3D printing methods for pharmaceutical manufacturing: opportunity and challenges. Curr Pharm Des. 2018;24(42):4949-4956. doi:10.2174/1381612825666181206121701.
10. Azad MA, Olawuni D, Kimbell G, Badruddoza AZM, Hossain S, Sultana T. Polymers for extrusion-based 3D printing of pharmaceuticals: a holistic materials-process perspective. Pharmaceutics. 2020;12(2):124. doi:10.3390/pharmaceutics12020124.
11. Shende P, Agrawal S. Integration of 3D printing with dosage forms: a new perspective for modern healthcare. Biomed Pharmacother. 2018;107:146-154. doi:10.1016/j.biopha.2018.07.167.
12. Goyanes A, Buanz ABM, Hatton GB, Gaisford S, Basit AW. 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. Eur J Pharm Biopharm. 2015;89:157-162. doi:10.1016/j.ejpb.2014.12.003.
13. Parhi R. A review of three-dimensional printing for pharmaceutical applications: quality control, risk assessment and future perspectives. J Drug Deliv Sci Technol. 2021;64:102571. doi:10.1016/j.jddst.2021.102571.
14. Kassem T, Sarkar T, Nguyen T, Saha D, Ahsan F. 3D printing in solid dosage forms and organ-on-chip applications. Biosensors (Basel). 2022;12(4):186. doi:10.3390/bios12040186.
15. Kapoor DU, Pareek A, Uniyal P, Prajapati BG, Thanawuth K, Sriamornsak P. Innovative applications of 3D printing in personalized medicine and complex drug delivery systems. iScience. 2025;28(10):113505. doi:10.1016/j.isci.2025.113505.
16. Keerikkadu M, Chennamsetty S, Shetty A, Tippavajhala VK, Rathnanand M. 3D-printed polypills for personalized medicine and precision oral drug delivery in pharmaceutical practice: a review. Int J Pharm X. 2025;11:100474. doi:10.1016/j.ijpx.2025.100474.
17. U.S. Food and Drug Administration. PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance: Guidance for Industry. Silver Spring (MD): FDA; 2004.
18. Liu P, Jin H, Chen Y, Wang D, Yan H, Wu M, et al. Process analytical technologies and self-optimization algorithms in automated pharmaceutical continuous manufacturing. Chin Chem Lett. 2024;35(3):108877. doi:10.1016/j.cclet.2023.108877.

19. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Q13: Continuous Manufacturing of Drug Substances and Drug Products. Geneva: ICH; 2022.
20. Gong S-J, Kim HR, Park Y-J, Kim J-E. Recent trends in continuous manufacturing and digitalization in pharmaceutical process development and manufacturing. J Pharm Investig. 2025;55(3):397-414. doi:10.1007/s40005-025-00728-8.
21. U.S. Food and Drug Administration. Artificial Intelligence in Drug Manufacturing. Discussion Paper. Silver Spring (MD): FDA/CDER; 2023.
22. Chalasani SH, Syed J, Ramesh M, Patil V, Pramod Kumar TM. Artificial intelligence in the field of pharmacy practice: a literature review. Res Social Adm Pharm. 2024;20(5):625-633. doi:10.1016/j.sapharm.2023.10.005.
23. Hatzimanolis J, Riley B, El-Den S, Aslani P, Zhou J, Chaar BB. Applications of artificial intelligence in current pharmacy practice: a scoping review. Res Social Adm Pharm. 2025;21(3):134-141. doi:10.1016/j.sapharm.2024.12.007.
24. U.S. Food and Drug Administration. Spritam (levetiracetam) NDA 207958: NDA Approval. Silver Spring (MD): FDA; 2015.
25. U.S. Food and Drug Administration. Considerations for the Use of Artificial Intelligence To Support Regulatory Decision-Making for Drug and Biological Products. Draft Guidance for Industry and Other Interested Parties. Silver Spring (MD): FDA; 2025.
26. U.S. Food and Drug Administration. Artificial Intelligence for Drug Development. Silver Spring (MD): FDA; current webpage, accessed 2026 Sep 8.