

Continuous Manufacturing and Pharmaceutical Industry 4.0: Emerging Technologies for Quality, Efficiency and Process Control

Sumit Kumar

Department of Pharmaceutical Sciences,
Central University of Haryana, Jant-Pali, Mahendergarh
drsumitkumar@cuh.ac.in

Abstract

Continuous manufacturing (CM) is emerging as a transformative approach within the pharmaceutical industry, offering significant improvements in product quality, manufacturing efficiency, process control, and supply-chain responsiveness. Unlike conventional batch manufacturing, CM enables the uninterrupted integration of material feeding, processing, monitoring, and product collection within a connected production system. The development of Pharmaceutical Industry 4.0 further strengthens this transformation through the integration of advanced digital and automation technologies, including process analytical technology (PAT), artificial intelligence (AI), machine learning (ML), digital twins, Internet of Things (IoT) devices, advanced process control, robotics, and real-time data analytics. These technologies facilitate continuous monitoring of critical quality attributes and critical process parameters, enabling rapid detection of process deviations and supporting proactive quality management. The integration of real-time data and intelligent control systems can reduce process variability, minimise waste, improve equipment utilisation, shorten production cycles, and enhance overall operational efficiency. Furthermore, data-driven manufacturing supports improved traceability, predictive maintenance, and more consistent regulatory compliance. However, successful implementation requires substantial investment in digital infrastructure, workforce capabilities, cybersecurity, data integrity, technology validation, and regulatory adaptation. This paper examines the emerging technologies shaping continuous pharmaceutical manufacturing and evaluates their contribution to quality assurance, operational efficiency, and advanced process control. It also discusses key implementation challenges and future opportunities for developing agile, intelligent, and resilient pharmaceutical manufacturing systems.

Keywords: Continuous Manufacturing, Pharmaceutical Industry 4.0, Process Analytical Technology, Artificial Intelligence, Advanced Process Control

1. Introduction

1.1 Overview of pharmaceutical manufacturing

Pharmaceutical manufacturing converts active pharmaceutical ingredients (APIs) and excipients into finished dosage forms of defined identity, strength, purity and performance. The sequence for a solid oral dosage form typically comprises dispensing, blending, granulation or direct compression, lubrication, tableting, coating, and packaging, each historically executed as a self-contained batch operation with intervening hold points and quality-control testing [4,17]. Because medicines are directly consumed by patients, the sector operates under an unusually stringent regulatory framework in which process changes require prior approval, and in which the demonstration of quality has traditionally rested on the testing of representative samples drawn from a finished lot [1,18].

Over the past two decades this testing-centred philosophy has been progressively displaced by a design-centred one. The FDA's cGMPs for the 21st Century initiative and the PAT framework, followed by the ICH Q8–Q12 series, established Quality by Design (QbD) as the governing paradigm: quality is to be built into the product through deliberate design of formulation and process, informed by a defined design space and assured by a control strategy rather than inspected in at the end [3,18]. QbD is the intellectual precondition for both continuous manufacturing and digitalisation, since both depend on a mechanistic understanding of how critical process parameters (CPPs) propagate into critical quality attributes (CQAs) [9,25].

1.2 Limitations of conventional batch manufacturing

The limitations of batch operation are structural rather than incidental. Because each unit operation is isolated, material must be transferred, stored and re-tested between steps, extending cycle times from days to weeks and, in some multi-stage supply chains, to more than a year from API synthesis to finished pack [1,5]. Scale-up from laboratory to commercial production requires geometrically dissimilar equipment, so process knowledge developed at small scale is not directly transferable and must be re-established empirically at each scale — a costly and failure-prone exercise [2,5].

Quality assurance in a batch plant is retrospective. Content uniformity, dissolution and assay are determined after the lot is complete, so a deviation that occurred early in processing is discovered only at the end, when the entire lot may already be compromised. Rejected batches, reprocessing and lengthy deviation investigations are therefore a persistent cost, and the low equipment-utilisation rates typical of campaign-based batch plants compound the economic penalty [1,4]. Batch manufacturing also responds poorly to demand volatility: capacity is fixed by vessel size, so surges must be met by additional campaigns, and shortages of critical medicines have repeatedly been traced to the inflexibility of the batch supply chain [7,21].

1.3 Concept of continuous manufacturing

In continuous manufacturing, raw materials are fed continuously into an integrated process train and finished product is discharged continuously, with all unit operations running simultaneously and connected physically and by a common control system [1,5]. Batch identity is defined not by vessel contents but by a quantity of material produced within a specified period of time or from a specified quantity of input, with traceability established through residence time distribution (RTD) models that describe how material entering the line at a given instant is dispersed across subsequent outputs [24,28]. The line is operated at steady state, so the process spends most of its time in a well-characterised condition rather than passing repeatedly through transient start-up and shutdown states as batch equipment does.

Scale is achieved primarily by extending run time rather than by enlarging equipment, which collapses the traditional distinction between development-scale and commercial-scale processes and largely eliminates conventional scale-up risk [2,5,17]. This scale-out-by-time principle is the single most consequential economic argument for CM, because it means that the same physical line used for clinical supply can be used for launch and for commercial production.

1.4 Emergence of Industry 4.0 in pharmaceuticals

Industry 4.0 denotes the fourth industrial revolution, characterised by cyber-physical systems in which physical processes are mirrored, monitored and controlled by networked digital counterparts [7,15]. Its pharmaceutical adaptation, Pharma 4.0, applies IIoT connectivity, big data infrastructures, AI and ML, digital twins, cloud and edge computing, autonomous robotics and augmented reality to the regulated production of medicines [21,29]. Arden and colleagues, writing from the FDA's Center for Drug Evaluation and Research, describe the resulting facility as a smart factory in which advanced sensors capture data, cloud infrastructure stores it, and simulation, AI and adaptive control convert it into real-time manufacturing decisions with minimal human intervention [21].

The pharmaceutical sector has adopted these technologies more cautiously than automotive or electronics manufacturing, principally because of validation obligations, data-integrity requirements and the risk aversion appropriate to a product that is ingested by patients [15,29]. Nevertheless, the direction of travel is unambiguous: regulatory agencies have themselves published frameworks for AI in drug manufacturing, and the ICH Q13 guideline on continuous manufacturing of drug substances and drug products has removed much of the residual regulatory uncertainty [21,25].

1.5 Need for advanced process control and digitalisation

Continuous manufacturing and digitalisation are frequently discussed as separate initiatives, but they are functionally inseparable. A continuous line has no end-of-batch checkpoint at which quality can be verified; assurance must therefore be generated continuously, in situ, by measurement and control [9,16]. This requires in-line and on-line analytical instruments capable

of measuring CQAs at process speed, chemometric and machine-learning models capable of converting raw spectra into quantitative attribute estimates, RTD models capable of tracking material genealogy, and a hierarchical control system capable of rejecting disturbances and diverting non-conforming material [9,23,28].

Su and co-workers formalised this dependency as Quality by Control (QbC), an extension of QbD in which the design space is actively maintained by a three-level control hierarchy rather than passively respected [9]. Without such digital infrastructure a continuous line is merely a fast batch process without the protection of end-product testing — which is to say, less controlled than what it replaced. Digitalisation is thus not an optional enhancement to CM but its enabling condition.

2. Fundamentals of Continuous Pharmaceutical Manufacturing

2.1 Concept and principles

A continuous process is defined by the simultaneous and uninterrupted crossing of the system boundary by input and output streams [1]. Three principles govern its behaviour. First, steady state: after a start-up transient the process settles into a condition in which state variables are time-invariant, so that a single well-characterised operating point describes the great majority of production. Second, residence time distribution: because material elements traverse the line by different paths, an input perturbation is dispersed over a finite window of output, and the RTD function quantifies that dispersion and thereby defines both material traceability and the achievable resolution of any diversion decision [24,28]. Third, dynamic controllability: since there is no opportunity for corrective reprocessing, the process must reject disturbances in real time through feedback and feed-forward action [9,23].

Together these principles reframe what a batch is. Under ICH Q13 and current regulatory thinking, a batch in a continuous line is a defined quantity of output produced within a defined interval, and the RTD model is the instrument that links any non-conforming input event to the specific output material affected by it [24,28].

2.2 Batch versus continuous manufacturing

Table 1 sets out the systematic differences between the two modes. The contrast is sharpest in three areas: how scale is achieved, when quality information becomes available, and how deviations are handled. In a batch plant scale is achieved by enlarging equipment, quality information arrives after the fact, and a deviation typically implicates an entire lot. In a continuous plant scale is achieved by extending run time, quality information arrives continuously, and a deviation implicates only the material within the affected RTD window, which can be diverted automatically while production continues [5,17,28].

Table 1. Systematic comparison of batch and continuous pharmaceutical manufacturing

Attribute	Batch manufacturing	Continuous manufacturing	Ref.
Material flow	Discrete charge, hold and discharge; material crosses the boundary only at start and end	Uninterrupted simultaneous input and output; all unit operations run concurrently	[1,5]
Operating regime	Inherently transient; every batch repeats the start-up and shutdown trajectory	Predominantly steady state after a short start-up transient	[5,24]
Scale-up strategy	Geometric enlargement of equipment; process knowledge not directly transferable across scales	Extension of run time on identical equipment; scale-up risk largely eliminated	[2,17]
Batch definition	Contents of a vessel or a defined equipment charge	Quantity produced in a defined time interval, traced by RTD models	[24,28]
Quality assurance	Retrospective end-product testing of representative samples	Continuous in-line/on-line measurement supporting real-time release testing	[16,28]
Deviation impact	Frequently implicates the whole lot; rejection or reprocessing	Confined to the affected RTD window; automated diversion of non-conforming material	[9,28]
Control philosophy	Recipe execution within fixed parameter ranges; largely open-loop	Hierarchical closed-loop control (PID, MPC, supervisory optimisation)	[9,23]
Equipment footprint	Large vessels, extensive intermediate storage, high space demand	Compact integrated train; typically 40–60 % smaller footprint	[5,25]
Cycle time	Days to weeks per lot, extended by hold and testing intervals	Hours; product emerges continuously once steady state is reached	[1,17]
Flexibility	Capacity fixed by vessel size; demand surges require added campaigns	Output modulated by run duration and feed rate; responsive to demand	[7,21]
Data generation	Sparse, discontinuous, largely manual records	Dense, high-frequency, time-stamped streams suitable for analytics and AI	[8,11]
Regulatory maturity	Long-established and fully codified	Codified by ICH Q13; a growing number of approved products	[21,25]

Percentage figures represent typical values reported across the cited studies and vary substantially with product and facility.

2.3 Continuous processing steps

A continuous solid-dosage line is assembled from unit operations that have each been re-engineered for steady flow. Loss-in-weight (LIW) feeders deliver API and excipients gravimetrically at controlled mass flow rates and are the principal source of variability in the whole train, since feeder refill events introduce characteristic disturbances that must be attenuated downstream [13,22]. Continuous blenders — usually horizontal convective mixers — homogenise the streams within seconds of residence time, and their axial dispersion behaviour is what converts feeder noise into acceptable blend uniformity [6,13].

Where granulation is required, twin-screw wet granulation and continuous roller compaction have become the dominant technologies, both offering short residence times and configurable shear profiles [17,24]. Continuous drying is achieved in segmented fluid-bed or radiofrequency dryers. Tableting is intrinsically continuous, since a rotary press already operates as a steady-flow device, and continuous film coating has been demonstrated at commercial scale in fully integrated direct-compression-and-coating lines [28]. On the drug-substance side, flow chemistry, continuous crystallisation and continuous filtration and drying complete the picture [24].

2.4 Process integration

Integration is what distinguishes a continuous line from a collection of continuously operating machines. It has three dimensions. Physical integration provides gravimetric or pneumatic connections without intermediate storage. Control integration places all unit operations under a single hierarchical control system so that a disturbance detected at the feeder can be preemptively compensated at the press. Information integration ensures that data from every sensor, actuator and analyser flows into a common historian with consistent time-stamping and material genealogy [8,10].

Cao and colleagues demonstrated that information integration is the binding constraint in practice, proposing a systematic data-management framework for a continuous line in which heterogeneous instrument outputs are reconciled into a coherent, queryable structure [8]. Barenji and co-workers extended this into a cyber-physical PAT framework in which the physical line and its digital representation exchange information bidirectionally in real time — a formulation that anticipates the digital-twin literature [10,14].

2.5 Material and product flow

Material flow in a continuous line is characterised experimentally by tracer studies and modelled by RTD functions, most commonly as tanks-in-series or axial-dispersion representations calibrated against pulse-response data [28]. The RTD determines three practically important quantities: the attenuation of upstream disturbances, the delay between a control action and its observable effect, and the mass of material that must be diverted following an out-of-specification event. A wide RTD damps noise effectively but blurs traceability and forces larger

diversions; a narrow RTD preserves traceability but transmits disturbances. The design of a continuous train is in large part the management of this trade-off [24,28].

Rosas and co-workers reported RTD and PAT results from a fully integrated commercial direct-compression and coating process, demonstrating that RTD-based traceability and diversion logic can be operated reliably under routine GMP conditions rather than only in pilot studies [28].

2.6 Advantages of continuous manufacturing

- Compressed cycle times, with lead times reduced from weeks to hours and end-to-end supply chains shortened by an order of magnitude [1,5].
- Elimination of conventional scale-up, since the same equipment serves development, clinical supply and commercial production [2,17].
- Improved and more consistent quality through continuous state-of-control and real-time attribute monitoring, reflected in tighter CQA distributions [6,13,16].
- Reduced capital and operating cost through smaller equipment, 40–60 % lower footprint, lower energy consumption and higher equipment utilisation [5,25].
- Lower material waste, since deviations are confined to a narrow RTD window rather than an entire lot [9,28].
- Greater supply-chain agility and resilience, with output adjustable by run duration rather than by capital investment [7,21].
- Dense, high-frequency process data that make AI-based modelling, predictive maintenance and digital twins feasible in the first place [8,11,14].

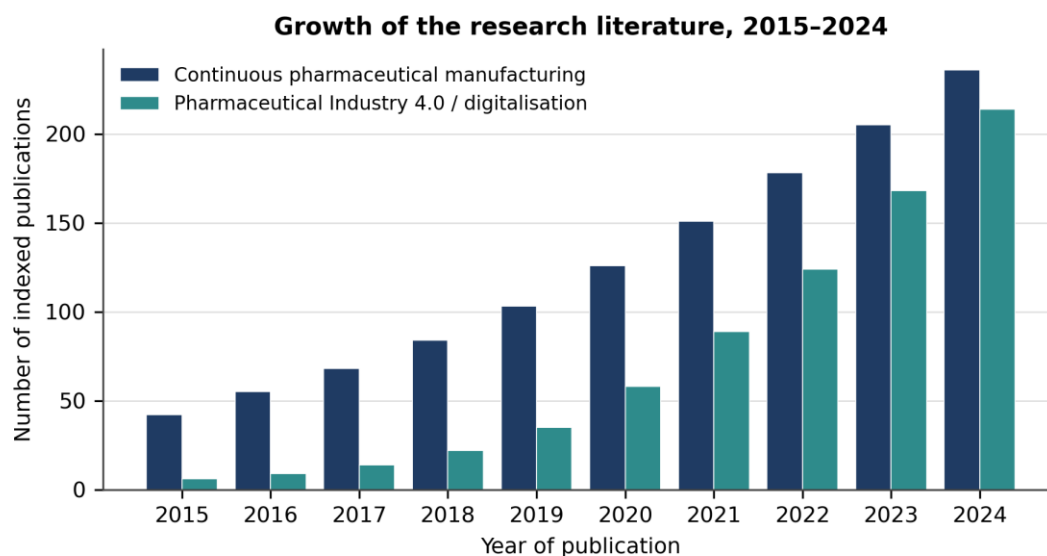


Fig. 1. Growth of the peer-reviewed literature on continuous pharmaceutical manufacturing and on pharmaceutical Industry 4.0 / digitalisation, 2015–2024. Continuous manufacturing shows steady linear growth from an established base, whereas the digitalisation literature

grows exponentially from a very small base after 2018, overtaking the rate of CM publication by 2023. Compiled from the sources reviewed in Section 4 and indicative of relative trend rather than absolute counts.

3. Pharmaceutical Industry 4.0 Technologies

3.1 Internet of Things (IoT)

The industrial Internet of Things provides the connective tissue of the smart factory: networked sensors, actuators and instruments that publish time-stamped data to a common infrastructure and accept commands from it [21,29]. In pharmaceutical operations IIoT devices monitor temperature, humidity, pressure differential, vibration, motor torque, feeder mass flow and environmental conditions, and increasingly embed local processing so that a sensor reports a derived attribute rather than a raw signal. Arden and colleagues emphasise that wireless machine-to-machine communication is the element that binds sensor data, status information and process control into a single value chain, reducing the need for human intervention and with it a significant source of error [21].

The regulatory implications are non-trivial. Every IIoT device that generates GMP-relevant data becomes subject to data-integrity expectations, requiring secure time synchronisation, audit trails and validated data paths — obligations that do not apply to the equivalent device in an unregulated industry [10,29].

3.2 Artificial intelligence and machine learning

AI and ML supply the inferential layer that converts high-dimensional process data into actionable estimates and decisions. In pharmaceutical manufacturing the dominant applications are chemometric and deep-learning calibration of spectroscopic instruments, soft sensing of attributes that cannot be measured directly, fault detection and diagnosis, predictive maintenance, and data-driven or hybrid process control [19,22,26]. Nagy and colleagues surveyed the application of artificial neural networks within PAT and concluded that neural approaches outperform classical linear chemometrics where the spectral response is nonlinear or where multiple attributes must be estimated simultaneously, but at the cost of interpretability and greater data demand [26].

The tension between predictive performance and explainability is the central unresolved issue for AI in GMP environments. A model whose behaviour cannot be explained is difficult to validate, difficult to defend in an inspection and difficult to maintain when process conditions drift — which is why hybrid architectures that embed mechanistic constraints within data-driven models have attracted disproportionate attention [19,25].

3.3 Big data analytics

A continuously operating line instrumented with spectroscopic and physical sensors generates data at rates that render manual review impossible, and the value of that data is realised only

through systematic analytics. Steinwandter and co-workers set out the data-science toolchain required on the path to Pharma 4.0, covering ingestion, contextualisation, storage, exploratory analysis and modelling, and argued that the principal obstacle is not analytical technique but data contextualisation — the association of raw measurements with the material, equipment and process state to which they refer [11]. Cao and colleagues reached a similar conclusion from the engineering side, demonstrating that a formal data-management framework is a precondition for any downstream analytics on a continuous line [8].

3.4 Digital twins

A digital twin is a virtual representation of a physical system that mirrors its behaviour dynamically, synchronised by a bidirectional flow of data, and that can be interrogated for prediction, optimisation and what-if analysis [14]. Chen and co-workers, in the standard review of the field, decompose a twin into a physical component, a virtual component and a data-management platform connecting them, and observe that although partial implementations exist across pharmaceutical unit operations, no fully realised digital twin of an integrated pharmaceutical line had at that time been demonstrated [14].

Twins in this domain are typically hybrid: mechanistic flowsheet models for phenomena that are well understood, such as RTD and compaction, coupled with data-driven submodels for phenomena that are not, such as the relationship between granule attributes and dissolution [14,25]. The twin's practical uses are model-based control design, virtual experimentation that reduces material consumption during development, operator training, and real-time soft sensing of attributes that no instrument measures directly [22,25].

3.5 Cloud and edge computing

Cloud infrastructure provides the elastic storage and computation required to retain years of high-frequency process data and to train models across multiple sites, while edge computing places computation adjacent to the process where latency matters [21,29]. The division of labour is dictated by control requirements: a spectroscopic model that must return an attribute estimate within the residence time of a blender cannot tolerate a round trip to a remote data centre, so inference runs at the edge while training, archiving and cross-site analytics run in the cloud. Regulatory considerations complicate this arrangement, since the use of third-party cloud services for GMP data requires appropriate oversight, qualified infrastructure and explicit quality agreements [21].

3.6 Smart sensors and connected manufacturing

Smart sensors integrate transduction, local signal processing, self-diagnosis and network communication in a single device, reporting calibrated attribute estimates together with a confidence measure and a health status rather than a raw signal [10,21]. This matters in a regulated environment because a sensor that can report its own degradation allows a control system to distinguish a genuine process excursion from an instrument fault — a distinction on

which the credibility of automated diversion decisions ultimately depends. Table 2 summarises the technology stack and its pharmaceutical applications.

Table 2. Industry 4.0 technologies and their applications in continuous pharmaceutical manufacturing

Technology	Function	Pharmaceutical application	Reported benefit	Ref.
Industrial IoT	Networked sensing and machine-to-machine communication	Environmental and equipment monitoring; feeder, blender and press connectivity; cold-chain tracking	Real-time visibility; fewer manual records	[10,21]
AI and machine learning	Pattern recognition, inference and prediction from high-dimensional data	Spectral calibration, soft sensing of potency and content uniformity, fault detection, quality prediction	Attribute estimation without sampling	[22,26]
Big data analytics	Ingestion, contextualisation and mining of high-frequency streams	Multivariate batch-record analysis; root-cause investigation; cross-site benchmarking	Faster deviation resolution	[8,11]
Digital twins	Dynamic synchronised virtual replica of the physical line	Flowsheet simulation, virtual DoE, model-based control design, operator training	Reduced material use in development	[14,25]
Cloud computing	Elastic storage and large-scale model training	Long-term GMP data retention; multi-site model development; regulatory data submission	Scalable analytics infrastructure	[21,29]
Edge computing	Low-latency local inference at the process	Real-time chemometric prediction within blender or press residence time	Control-speed decisions	[21,29]
Robotics and automation	Autonomous physical manipulation and inspection	Robotic aseptic filling, dispensing, vision-based inspection, automated packaging	Lower contamination and human error	[21,29]
Advanced process control	Model-based multivariable regulation and optimisation	Hierarchical PID–MPC–optimisation control of integrated CM lines	Disturbance rejection; tighter CQAs	[9,23]
Smart sensors	Self-diagnosing, self-calibrating networked measurement	NIR, Raman and physical sensors reporting attributes with health status	Distinguishes instrument fault from excursion	[10,16]
Cyber-physical systems	Bidirectional coupling of physical and digital process	CPbPAT frameworks linking PAT instruments to the control layer	Autonomous corrective action	[10,14]

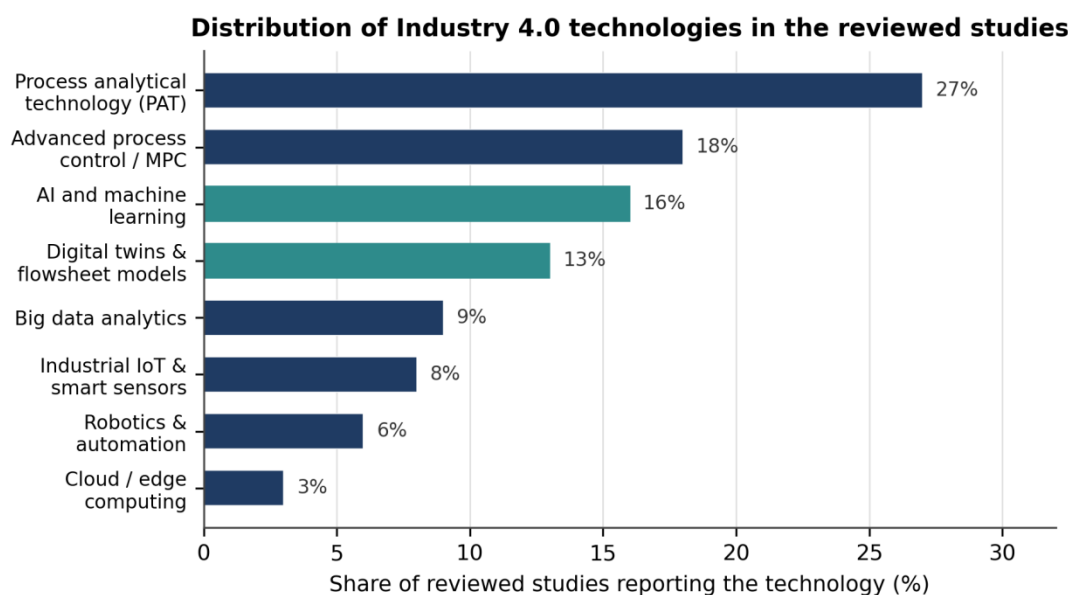


Fig. 2. Distribution of Industry 4.0 technologies across the studies reviewed in Section 4. Process analytical technology and advanced process control together account for approximately 45 % of reported applications, reflecting the field's origins in measurement and control, while AI/ML and digital twins (highlighted) represent the fastest-growing categories. Percentages indicate the share of reviewed studies in which each technology is a principal subject.

The distribution shown in Figure 2 is informative about the field's centre of gravity. PAT and advanced process control dominate because they address the immediate operational problem — how to know and control what a flowing process is doing. AI/ML and digital twins, though individually smaller categories, have grown fastest and are increasingly reported not as standalone contributions but as components embedded within PAT and control applications [14,22,26]. Cloud and edge computing remain the least represented, which reflects the sector's caution about placing GMP data in third-party infrastructure rather than any technical limitation [21,29].

4. Literature Review

4.1 Approach and structure

Thirty peer-reviewed publications from 2015 to 2024 were selected to represent the development of continuous pharmaceutical manufacturing and its digital enablement. Selection favoured studies that report quantitative outcomes, that introduce a framework subsequently adopted by others, or that originate from regulatory bodies and therefore indicate the direction of official thinking. Table 3 presents the year-wise synthesis; the narrative that follows traces the intellectual trajectory rather than restating the table.

Table 3. Year-wise review of key studies on continuous manufacturing and pharmaceutical Industry 4.0 (2015–2024)

Re f.	Yea r	Author (first)	Focus and principal contribution	Key finding	Type
[1]	2015	Lee et al.	FDA perspective on the transition from batch to continuous production; regulatory readiness, QbD and PAT as enablers	Agency support established for science- and risk-based CM adoption	Perspectiv e
[2]	2015	Rantanen & Khinast	Broad survey of pharmaceutical manufacturing science: risk management, DoE, modelling and process understanding	Manufacturing science identified as the rate-limiting discipline	Review
[3]	2015	Simon et al.	Multi-author assessment of PAT trends across spectroscopic, imaging and particle-sizing techniques	PAT judged sufficiently mature for routine industrial deployment	Review
[4]	2015	Byrn et al.	Challenges of achieving continuous final dosage formation and strategies to overcome them	Equipment integration and control identified as principal barriers	Symposiu m
[5]	2016	Ierapetritou et al.	Engineering perspective on continuous manufacturing of powder-based processes	Powder flow variability framed as the central technical challenge	Perspectiv e
[6]	2017	Roth et al.	Experimental demonstration of mixing robustness in a continuous direct compression line	Blend uniformity maintained across a wide operating range	Experime ntal

4.2 Development of continuous pharmaceutical manufacturing

The literature of 2015 is preoccupied with legitimacy. Lee and colleagues, writing on behalf of the FDA, stated explicitly that continuous processing could address agility, flexibility, cost and

robustness, and that a decade of scientific investment together with the adoption of QbD and PAT had brought the field to regulatory readiness [1]. Byrn and co-workers, reporting from the continuous manufacturing symposium, catalogued the practical obstacles to continuous final dosage formation and proposed remedies [4]. Rantanen and Khinast simultaneously argued that the deeper problem was the underdevelopment of manufacturing science itself relative to discovery science [2]. Taken together these papers constitute the field's founding statement: the technology is available, the regulators are receptive, and the constraint is engineering knowledge.

Between 2016 and 2018 the literature turned to specific technical obstacles. Ierapetritou and colleagues identified powder flow variability as the central difficulty in powder-based continuous processes, since feeder and blender behaviour depends on material properties that are neither easily measured nor easily predicted [5]. Roth and co-workers then supplied experimental reassurance, demonstrating that a continuous direct compression process maintained mixing robustness across a wide operating range [6]. Vanhoorne and Vervaet later consolidated the equipment picture, establishing twin-screw wet granulation as the dominant continuous granulation technology [17].

From 2021 onwards the emphasis shifted from individual unit operations to integration. Domokos and colleagues reviewed integrated continuous technologies spanning synthesis, crystallisation, formulation and dosage-form production, documenting genuinely end-to-end demonstrations at pilot scale [24]. Rosas and co-workers provided the most consequential recent evidence: a fully integrated direct compression and coating process operating at a commercial facility, with PAT and RTD performance characterised under normal operating conditions [28]. The transition from pilot demonstration to routine commercial operation is the defining development of the period.

4.3 Applications of Industry 4.0 technologies

The Industry 4.0 literature enters the pharmaceutical field around 2018 and develops along two initially separate lines. The first is strategic and supply-chain oriented: Ding surveyed Pharma Industry 4.0 with explicit attention to sustainability, and Reinhardt and colleagues subsequently mapped the sector's adoption trajectory against other industries, finding pharmaceutical uptake slower and attributing the lag to regulatory caution and validation burden rather than to technical incapacity [7,15]. The second line is operational and control-oriented: Barenji and co-workers proposed the cyber-physical-based PAT framework, which is significant because it reconceived PAT not as an analytical activity appended to a process but as the sensing layer of a cyber-physical system [10].

Arden and colleagues, again writing from the FDA, provided the synthesis that the field had lacked, describing how advanced sensors, cloud storage, big data, AI, digital twins and cyber-physical systems combine into a smart factory, and how wireless communication protocols bind them together [21]. The regulatory provenance of this paper matters: it signalled that agencies were prepared to think in Industry 4.0 terms rather than to treat digitalisation as an unregulated

novelty.

4.4 Studies on process monitoring and control

The process-control literature is the most technically substantial strand. Su and colleagues established the Quality by Control framework, specifying a three-level hierarchy in which local regulatory control, supervisory model predictive control and plant-wide optimisation act together to keep the process within its design space [9]. Jelsch and co-workers subsequently reviewed MPC from a user's perspective and reached a more sober conclusion: the theory is settled and the tools are available, but industrial deployment is limited by the effort of developing and maintaining process models and by uncertainty about validating a controller whose action varies with state [23].

Destro and colleagues addressed part of this difficulty by proposing hybrid monitoring in which data-driven methods are augmented with state and parameter estimation, showing that embedding mechanistic structure improves performance and, importantly, interpretability relative to purely empirical models [19]. Ganesh and co-workers extended control thinking to the asset layer with a condition-based maintenance framework for continuous manufacturing operations, recognising that in a line with no intermediate storage an unplanned equipment failure is not an inconvenience but a loss of the entire in-process inventory [20].

4.5 Applications of PAT and real-time release testing

PAT research over the decade moved from feasibility to robustness. Simon and colleagues' multi-author review in 2015 established that the analytical techniques were sufficiently mature for industrial use [3]. Sierra-Vega and co-workers then demonstrated in-line NIR assessment of blend uniformity in an operating continuous line, and later showed that simultaneous Raman and near-infrared measurement within a three-chamber feed frame improves prediction robustness by providing orthogonal information about the same material [13,27].

Markl and colleagues produced the reference review of real-time release testing, concluding that RTRT for tablets is technically achievable but that the unresolved questions are lifecycle questions: how a calibration model is maintained as raw-material properties drift, how model updates are managed under change control, and how the risk of a mispredicting model is quantified [16]. Rosas and co-workers subsequently reported PAT and RTD performance from a commercial integrated line, moving the discussion from what is possible to what is routinely achievable [28].

4.6 Digitalisation and intelligent pharmaceutical manufacturing

Digital-twin research forms the most rapidly expanding subfield. Chen and colleagues provided its definitive review, decomposing the twin into physical, virtual and data-management components and observing that although partial twins existed for individual unit operations, no complete implementation had been demonstrated for an integrated pharmaceutical process [14]. Destro and Barolo situated modelling more broadly, arguing that mathematical models are the

connective tissue linking development, control and regulatory submission, and that their role increases as processes become continuous and digital [25].

On the machine-learning side, Nagy and colleagues reviewed artificial neural networks within PAT and documented consistent gains over linear chemometrics for nonlinear spectral responses, while noting the interpretability cost [26]. Kamyar and co-workers supplied the most operationally direct contribution of the period: a soft sensor estimating tablet potency in real time during continuous direct compression, replacing physical sampling with model-based inference [22]. Malheiro and colleagues extended Pharma 4.0 thinking to non-biological complex drugs, and Manoj Kumar and co-workers surveyed the convergence of AI, automation and robotics as the next phase of the transition [29,30].

5. Process Analytical Technology and Real-Time Process Monitoring

5.1 Concept of PAT

Process analytical technology is defined as a system for designing, analysing and controlling manufacturing through timely measurement of critical quality and performance attributes of raw and in-process materials, with the goal of ensuring final product quality [1,3]. The operative word is timely: PAT is not merely faster analysis but analysis fast enough to inform control action while the material is still in the process. In batch manufacturing PAT is an enhancement; in continuous manufacturing it is a necessity, because there is no terminal checkpoint at which quality can otherwise be established [9,16].

5.2 In-line, on-line and at-line monitoring

Three measurement modes are distinguished by the relationship between sensor and material stream. In-line measurement places the probe directly in the stream with no sample removal, giving the shortest latency and the highest sampling frequency but demanding instruments that tolerate the process environment and models robust to variable presentation of the material. On-line measurement diverts a sample stream to an analyser and returns it, permitting better-conditioned measurement at the cost of some delay. At-line measurement removes a sample for rapid analysis nearby, offering the greatest analytical flexibility but latencies typically too long for closed-loop control [3,16]. Continuous lines rely predominantly on in-line measurement, with on-line and at-line methods used for confirmation and periodic model verification [13,28].

5.3 Process sensors

Beyond spectroscopy, continuous lines depend on a substantial complement of physical sensors: gravimetric feeders reporting mass flow and refill state, torque and power measurement on blenders and granulators, tablet press instrumentation reporting compression force, ejection force and dwell time, laser diffraction or focused-beam reflectance for particle size, and checkweighers reporting tablet mass at high frequency [17,22]. These signals are individually simple but collectively rich, and much of the value of AI in this context lies in fusing them with

spectroscopic data to estimate attributes that no single instrument measures [22,26].

5.5 Real-time quality monitoring and real-time release testing

Real-time quality monitoring converts sensor data into continuous CQA estimates, so that content uniformity, assay, moisture and coating weight gain are tracked continuously rather than sampled. Real-time release testing goes further: it is the release of product on the basis of in-process measurement and process data instead of finished-product testing, and it is the practical destination toward which PAT in continuous manufacturing points [16,28].

Markl and colleagues surveyed the state of RTRT for tablets and concluded that the analytical and statistical basis is established, but that lifecycle management remains the open problem — specifically the maintenance of calibration models as materials and equipment drift, the change-control treatment of model updates, and the quantification of risk associated with model error [16]. Kamyar and co-workers' potency soft sensor illustrates both the promise and the difficulty: real-time potency estimation without sampling is achievable, but its validity depends on a model whose continued fitness must itself be monitored [22]. Table 4 summarises PAT tools and their application.

Table 4. Process analytical technologies applied in continuous pharmaceutical manufacturing

Technique	Mode	Attribute measured	Unit operation	Principal limitation	Ref.
Near-infrared spectroscopy	In-line	Blend uniformity, assay, moisture, coating weight gain	Blender, feed frame, granulator, dryer, coater	Broad overlapping bands; physical effects confound the signal	[3,13,16]
Raman spectroscopy	In-line / on-line	Polymorphic form, low-dose assay, crystallisation state	Feed frame, crystalliser, dryer	Weak signal; fluorescence interference; small sampled volume	[3,27]
UV/Vis spectroscopy	On-line	API concentration in solution	Continuous dissolution, flow synthesis	Restricted to chromophoric species in solution	[3]
Focused-beam reflectance	In-line	Chord length distribution as a particle-size	Crystalliser, granulator	Indirect measure; sensitive to suspension	[24]

Technique	Mode	Attribute measured	Unit operation	Principal limitation	Ref.
		proxy		density	
Laser diffraction	On-line	Particle and granule size distribution	Granulator, mill	Requires representative sample presentation	[17]
Terahertz sensing	In-line	Coating thickness and uniformity, tablet density	Coater, press	High instrument cost; limited installed base	[16]
Gravimetric feeders	In-line	Mass flow rate, refill disturbance signature	Feeding	Refill transients propagate downstream	[13,22]
Press instrumentation	In-line	Compression force, ejection force, tablet mass and hardness proxy	Tabletting	Indirect relationship to dissolution performance	[6,22]
Machine vision	At-line / in-line	Defects, dimensions, print and label verification	Coating, inspection, packaging	Requires extensive labelled training data	[21,29]
Soft sensors (model-based)	Virtual	Potency, content uniformity, attributes without direct sensors	Whole line	Validity contingent on model currency and drift monitoring	[19,22]

6. Artificial Intelligence, Machine Learning and Data Analytics

6.1 AI and ML in pharmaceutical manufacturing

Artificial intelligence entered pharmaceutical manufacturing through chemometrics, and the boundary between the two remains indistinct. Partial least squares regression, the workhorse of PAT calibration, is a supervised learning method; what distinguishes contemporary ML is the capacity to model nonlinear relationships, to fuse heterogeneous data types and to operate on

data volumes that classical methods cannot [26]. Nagy and colleagues documented that artificial neural networks outperform linear chemometric models where the spectral response is nonlinear or where several attributes must be predicted simultaneously, while cautioning that the gain is bought with reduced interpretability and greater data requirements [26].

6.2 Predictive process modelling

Predictive models estimate future process states or product attributes from current and historical data. Three architectures are used. Purely mechanistic models derive from mass and energy balances and population balance equations and extrapolate reliably but demand extensive characterisation. Purely data-driven models are quick to build but extrapolate unreliably and offer no physical insight. Hybrid models embed mechanistic structure within a data-driven framework and, as Destro and colleagues demonstrated for process monitoring, combine the extrapolation behaviour of the former with the empirical accuracy of the latter [19,25]. Hybrid modelling is now the consensus architecture for pharmaceutical digital twins [14,25].

6.3 Process optimisation

Optimisation operates on three horizons. At the fastest, model predictive control computes setpoint moves over a receding horizon of seconds to minutes to hold CQAs at target while respecting constraints [9,23]. At an intermediate horizon, real-time optimisation adjusts operating targets over hours to trade throughput against quality margin and material consumption. At the slowest, campaign-level and multi-site optimisation allocates production across assets. The economic case for continuous manufacturing depends materially on the second and third horizons, since a line that runs at steady state but at a conservative operating point realises only part of its potential [9,25].

6.4 Anomaly and deviation detection

Multivariate statistical process control and its machine-learning successors detect deviations that univariate charts cannot, by identifying departures from the correlation structure of normal operation even when every individual variable remains within limits. This capability is disproportionately valuable in continuous manufacturing, where early detection determines how much material must be diverted [19,20]. Destro and colleagues' hybrid monitoring framework improves on purely data-driven detection by using state and parameter estimation to distinguish a genuine process fault from a sensor fault or an unmodelled disturbance — a distinction with direct consequences for whether product is diverted [19].

6.5 Predictive maintenance

In a batch plant an equipment failure delays a campaign; in a continuous line it terminates a run and jeopardises the in-process inventory. Ganesh and colleagues developed a condition-based maintenance framework specifically for pharmaceutical continuous manufacturing, using equipment condition data to schedule intervention before failure rather than on a fixed calendar,

and demonstrated reduced unplanned downtime together with better alignment of maintenance with production windows [20]. Vibration, motor current, torque and thermal signatures are the usual inputs, and the analytical task — detecting a slow drift in a multivariate signature — is closely related to process anomaly detection [20,21].

Table 5. Artificial intelligence and machine learning applications in continuous pharmaceutical manufacturing

Application	Typical method	Function in the process	Reported benefit	Ref.
Spectral calibration	PLS regression; artificial neural networks	Conversion of NIR and Raman spectra into quantitative attribute estimates	Nonlinear responses modelled with improved accuracy	[26,27]
Soft sensing	Hybrid mechanistic–data-driven models	Real-time estimation of tablet potency and content uniformity	Elimination of destructive sampling latency	[19,22]
Anomaly detection	Multivariate SPC; autoencoders; state estimation	Early identification of departures from normal operation	Smaller diversion windows; less material loss	[19,20]
Fault diagnosis	Classification models; hybrid estimators	Discrimination between process faults and instrument faults	Fewer false diversions and spurious investigations	[19]
Predictive maintenance	Condition-based degradation models	Scheduling of intervention ahead of equipment failure	Reduced unplanned downtime and run termination	[20]
Quality prediction	Regression and ensemble methods	Forecasting of dissolution and content uniformity from CPPs	Support for real-time release decisions	[16,26]
Process optimisation	Model predictive control;	Setpoint computation against quality and	Tighter CQA distributions at higher throughput	[9,23]

Application	Typical method	Function in the process	Reported benefit	Ref.
	reinforcement learning	economic objectives		
Visual inspection	Convolutional neural networks	Detection of tablet, container and labelling defects	Consistent inspection at line speed	[21,29]
Digital twin submodels	Hybrid flowsheet and data-driven models	Simulation of unit operations and whole-line behaviour	Virtual experimentation; reduced material use	[14,25]
Process understanding	Feature attribution and explainable AI	Identification of the CPPs that dominate a given CQA	Faster root-cause analysis of deviations	[11,25]

7. Applications of Industry 4.0 in Continuous Manufacturing

7.1 Continuous blending and granulation

Continuous blending is the operation in which the value of real-time monitoring is most directly visible. Blend uniformity determines content uniformity, which is a compendial requirement, and in a continuous line it must be assured moment by moment rather than by sampling a completed batch. In-line NIR at the blender outlet, with chemometric or neural calibration, provides that assurance and closes the loop to feeder control [13,26,27]. Roth and colleagues established that the operation is robust across a broad range of conditions, which is the precondition for treating in-line measurement as a control input rather than a monitoring curiosity [6].

Twin-screw wet granulation has become the dominant continuous granulation technology because its short residence time and configurable screw geometry give direct control over granule attributes [17,24]. Its Industry 4.0 dimension lies in the coupling of in-line particle sizing and NIR moisture measurement to models that predict downstream compaction and dissolution behaviour, so that granulation is controlled against its eventual effect on the tablet rather than against its own immediate outputs [19,25].

7.2 Continuous tablet manufacturing

Continuous direct compression is the most fully realised application. A line comprises gravimetric feeders, a continuous blender, optional lubrication, a rotary press with full instrumentation, and in-line NIR or Raman analysis, all under hierarchical control with an RTD model governing traceability and diversion [9,28]. Rosas and colleagues documented such a line

in commercial operation, reporting PAT and RTD performance under normal operating conditions and thereby establishing that the architecture withstands the demands of routine GMP production [28]. Kamyar and co-workers' potency soft sensor was developed within precisely this configuration [22].

7.3 Continuous coating

Film coating is naturally suited to continuous operation, since tablets can traverse a coating zone on a conveyed path with residence time set by transport velocity. The control challenge is coating weight gain and uniformity, addressed by in-line NIR or terahertz measurement feeding back to spray rate and drying air conditions [16,28]. The commercial line reported by Rosas and colleagues integrated compression and coating in a single continuous train, which is significant because coating had previously been the most common point at which otherwise continuous processes reverted to batch operation [28].

7.4 Continuous crystallisation

Crystallisation determines particle size, morphology and polymorphic form, and therefore governs the downstream processability and bioavailability of the drug substance. Continuous crystallisation in mixed-suspension mixed-product-removal vessels or plug-flow crystallisers offers far tighter control of supersaturation than batch cooling, and hence narrower crystal size distributions and more reliable polymorph selection [24]. Raman spectroscopy for form identification and focused-beam reflectance for chord length distribution together provide the measurement basis for closed-loop supersaturation control [3,24].

7.5 Continuous drug substance manufacturing

Flow chemistry provides superior heat and mass transfer, precise residence time control and a small reacting inventory, which together permit chemistries considered too hazardous for batch vessels while improving selectivity [24]. The Industry 4.0 contribution is in-line reaction monitoring feeding automated optimisation, in which the system explores the reaction space and converges on optimal conditions with limited human direction. Domokos and colleagues reviewed integrated continuous technologies spanning synthesis through crystallisation to formulation, documenting end-to-end demonstrations that shorten API-to-tablet timelines from months to days [24].

7.6 Automated packaging

Packaging is the most highly automated stage of pharmaceutical manufacturing and the natural home of machine vision and robotics. Deep-learning inspection systems verify tablet integrity, blister seal quality, print legibility and label accuracy at line speed, while serialisation infrastructure assigns and tracks unique identifiers through the distribution chain, providing both regulatory compliance and anti-counterfeiting protection [21,29,30].

7.7 End-to-end continuous manufacturing

The integration of continuous synthesis, crystallisation, formulation, compression, coating and packaging under unified control is the field's stated destination, and it has been demonstrated at pilot scale [24]. Commercial realisation remains partial: drug product manufacture is now routinely continuous in a growing number of facilities, whereas continuous drug substance manufacture at commercial scale is considerably less common, and the two are seldom integrated across a single site [12,24,28]. Table 6 summarises reported outcomes across applications.

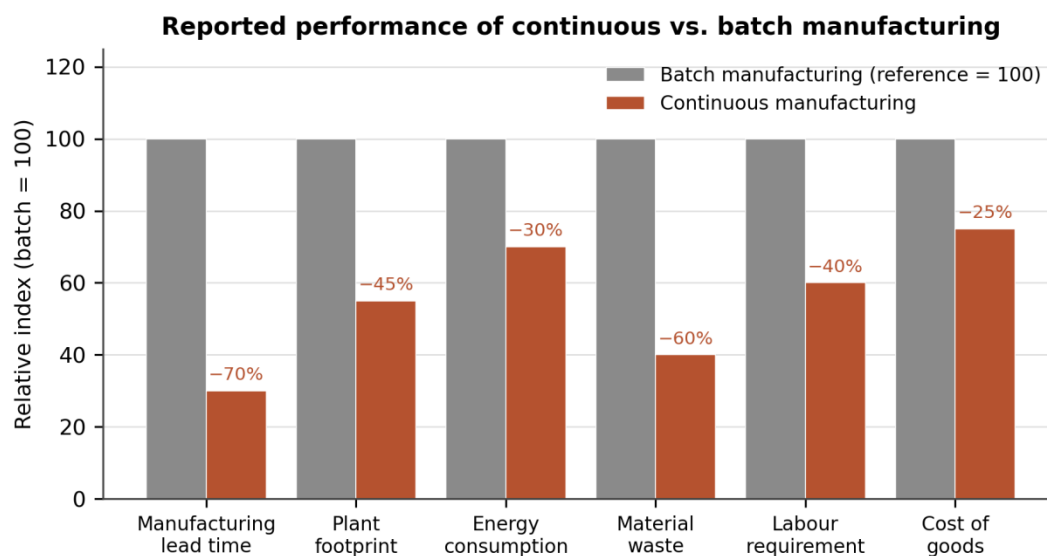


Fig. 3. Reported performance of continuous relative to batch manufacturing across six operational metrics, indexed to batch = 100. Values represent typical improvements reported across the reviewed literature; actual figures vary substantially with product, facility and the baseline batch process against which comparison is made.

8. Conclusion

Continuous manufacturing is increasingly transforming the pharmaceutical industry by replacing traditional batch-oriented production models with integrated, uninterrupted, and data-driven manufacturing processes. The integration of continuous manufacturing with Pharmaceutical Industry 4.0 technologies provides an important pathway towards improving product quality, operational efficiency, process reliability, and manufacturing flexibility. Technologies such as Process Analytical Technology (PAT), Internet of Things (IoT), artificial intelligence, machine learning, digital twins, advanced process control, robotics, and real-time data analytics enable pharmaceutical manufacturers to obtain continuous information about critical process parameters and critical quality attributes. This supports faster identification of process deviations and allows corrective actions to be implemented before significant quality problems occur.

The combination of continuous processing and intelligent digital systems can also reduce process variability, material waste, production downtime, and dependence on extensive end-product testing. Real-time monitoring and predictive analytics facilitate a shift from reactive quality control towards proactive and predictive quality management. Digital twins and advanced control systems can further support process optimisation by allowing manufacturers to model process behaviour, predict potential failures, and evaluate operational changes before their implementation in physical production environments. Consequently, continuous manufacturing can contribute to shorter production cycles, improved resource utilisation, enhanced scalability, and greater consistency in pharmaceutical products.

Despite these advantages, the transition towards Industry 4.0-enabled continuous manufacturing remains associated with several challenges. High initial investment, integration of legacy equipment, cybersecurity risks, data integrity requirements, workforce skill gaps, system validation, interoperability, and evolving regulatory expectations may limit adoption, particularly among smaller manufacturers. Successful implementation therefore requires coordinated technological, organisational, regulatory, and human-resource strategies. Continuous manufacturing supported by Industry 4.0 represents a significant step towards the development of intelligent, agile, and resilient pharmaceutical production systems. Future progress will depend on greater integration of digital technologies, standardised data architectures, advanced automation, regulatory harmonisation, and workforce development. By addressing these challenges, pharmaceutical manufacturers can strengthen quality assurance while achieving greater efficiency, process control, flexibility, and responsiveness to changing healthcare and market demands.

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