Review On Potential Of Continuous Manufacturing Approach In Improvement Of Product Quality

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Abstract

Continuous Manufacturing (CM) is transforming drug manufacturing with a more efficient, adaptable, and quality-oriented option compared to conventional batch operations. Here, this review sketches the key principles, advantages, and technology facilitators of CM, including Process Analytical Technology (PAT), real-time process control, and software integration. It also discusses the role of CM in product quality improvement. The emphasis is placed on using software tools for the implementation of a shift from batch to continuous operations such as PAT software, Manufacturing Execution Systems (MES), Supervisory Control and Data Acquisition (SCADA) systems, and simulation platforms. Additionally, the review covers the use of PAT and Quality by Design (QbD) frameworks in allowing real-time monitoring and release strategies. This review illustrates that CM not only decreases product variability and process control but also encourages cost efficiency, regulatory compliance, and personalized medicine. These developments eventually result in extensive pharmaceutical quality and supply chain responsiveness improvements.

Keywords: Continuous Manufacturing, Assessment of Quality Improvement, Implementation of PAT, Use of Software

Introduction

Continuous Manufacturing (CM) of pharmaceutical drug products is an innovative approach that differs from traditional batch manufacturing processes. CM enhances manufacturing flexibility and efficiency by interconnecting all production units. In this setup, raw materials are continuously fed into the initial unit at the beginning of the production line, while the final product is simultaneously released at the end. Research indicates that implementing CM necessitates advanced process control strategies to achieve a real-time understanding of the ongoing process state and to maintain consistent product quality within defined limits. These control strategies can be facilitated by suitable in-line and/or at-line Process Analytical Technologies (PAT), which provide immediate information about the process state and product quality. This information can be used in conjunction with control loops that allow real-time adjustments to critical process parameters. [1-3] However, experience shows that the

robustness of a CM process greatly depends on the specific product and formulation. This implies that the unique requirements of each product can greatly affect process design. For example, certain products may require stringent control over process parameters throughout granulation, drying, and tableting. Even minor deviations can significantly influence the quality of the final drug product; for instance, disintegration time can be compromised by producing excessive fine particles or overly coarse granules during granulation. Variations in the liquid-to-solid ratio during processing can contribute to these challenges, as highlighted in previous studies. Additionally, differing amounts of water during granulation can lead to polymorphic changes in the drug substance. Conversely, some products may not demand such stringent controls, as their formulations might demonstrate robustness to certain variations in the process.

Near Infrared Spectroscopy (NIRS) has emerged as a popular PAT tool in the pharmaceutical sector, valued for its safety, speed, and non-invasive nature, eliminating the need for sample preparation. The adoption of NIRS in pharmaceutical manufacturing received early support from the US Food and Drug Administration (FDA) as part of its PAT initiative in 2004. [2,4] Currently, NIRS is commonly used for raw material identification, in-line monitoring during processes such as blending, granulation, and drying, and troubleshooting. [5-10]

The primary aim of this paper is to propose a monitoring strategy for the CM production line. The study reviews three main sources of information: In-Process Controls (IPC), process parameters, and PAT values. To assess the robustness of the continuous process, a Design of Experiments was conducted using a formulation of a new product that is currently in development.

Continuous Manufacturing (CM):

Continuous manufacturing (CM) is a method of manufacturing products and pro cessing materials without interruption and with constant material feed and removal.

The concept of continuous processing has been around for quite some time and is widely utilized across various industries, including oil refining, chemical production, fertilizer manufacturing, paper, and food. One of the earliest examples of continuous processing can be found in the paper industry with the Fourdrinier paper machine, which was patented in 1799. Additionally, automotive manufacturing, specifically the assembly part, can also be considered a continuous process. The first assembly lines were introduced in the early twentieth century by Oldsmobile, followed by a more publicized implementation by Ford with the Model T several years later.

Advantages of Continuous Manufacturing in Pharmaceuticals: [11-14]

Continuous Manufacturing (CM) offers a transformative shift in how drugs are developed and produced, benefiting patients, manufacturers, and society at large.

1. Flexible Operations

CM enables rapid process adaptation using existing lines, allowing multiple product campaigns with varying durations. Selected steps like blending or granulation can run continuously, while others like coating may stay batch-based—offering hybrid flexibility.

2. Streamlined Supply Chain

By integrating production steps and reducing logistics between contract manufacturers, CM shortens lead times, cuts storage costs, and responds swiftly to urgent needs like pandemics or clinical trial transitions.

3. Agility & Minimal Scale-Up

Unlike traditional batch processes, CM minimizes or eliminates scale-up, using the same equipment from development to production. This reduces delays, avoids OoS batches, and suits small-volume or personalized therapies.

4. Real-Time Quality Control

Advanced sensors and control systems in CM ensure real-time monitoring of critical quality attributes (CQAs), enabling consistent output and real-time release (RTR) of products.

5. Decentralized & Mobile Production

CM facilities are compact and modular, allowing potential deployment in containers for local, military, or remote-area manufacturing. This decentralization could enhance access in underserved regions.

6. Personalized Medicine

CM supports individualized dosing—especially valuable in geriatrics—by customizing dose forms (e.g., capsule blending or 3D printing). While still in development, this concept shows promise for future care models.

7. Lower Costs & Space Requirements

CM lines combine multiple steps in a single space, reducing floor space by up to 80% and investment costs by up to 76%. Operational efficiency improves, with higher equipment utilization and less intermediate storage.

8. Improved Chemistry Pathways

Using micro-scale flow reactors, CM safely enables more efficient, selective, and exothermic chemistries previously unsuitable for large batch processes, expanding synthetic possibilities.

9. Societal & Environmental Benefits

CM lowers drug costs, reduces environmental impact, and supports high-tech job creation. It accelerates access to innovative dosage forms and improves overall medicine quality and affordability.

Table 1: Comparison between Continuous Manufacturing and Traditional Batch Manufacturing[11-13]

Subject	Continuous Manufacturing (CM)	Traditional Batch Manufacturing
Process Flow	Materials are fed and products are produced **continuously** in a connected process	Production occurs in **discrete steps** with clear start and end points
Production Time	**Faster** – Real-time operations without long waiting periods	**Slower** – Requires downtime between steps and for cleaning/validation
Scale-Up Requirements	**Minimal or none** – same equipment can be used for development and production	**Extensive** – scale-up needed from lab to commercial scale

Flexibility	High – can quickly adjust volume and switch between products	Low – fixed setup, slow to adapt to changes
Space & Equipment	**Compact** – multiple steps integrated into a smaller footprint	**Large** – separate rooms/equipment for each stage
Quality Control	**Real-Time Release (RTR)** with in-line monitoring (PAT tools)	**Post-production testing**; may lead to batch rejection
Waste and rework	Less – due to continuous monitoring and control	More – due to batch failures, reprocessing or discards
Cost Efficiency	Lower operating and capital costs in the long run	Higher costs due to inefficiency and manual operations
Supply Chain Responsiveness	Rapid response to market demand, suitable for emergencies	Slower response, vulnerable to delays
Regulatory Acceptance	Increasingly accepted (FDA/EMA support CM adoption)	Established and widely accepted
Technology Complexity	Requires sophisticated automation and real-time control systems	Less complex, but labour intensive
Suitability for Personalized Medicine	**Ideal** – supports on-demand or small-batch dosing	Not suitable – inefficient for low-volume customized doses

Assessment Quality improvement by Continuous Manufacturing:[11,12,15]

a. Real-Time Process Monitoring

PAT allows manufacturers to monitor quality in real time and make adjustments during production, rather than relying solely on end-product testing.

b. Reduced Product Variability

The adoption of CM minimizes variability due to its consistent operating conditions, leading to superior product uniformity compared to batch production.

c. Enhanced Process Control

Improved automation and integrated control mechanisms in CM enable tighter control of process variables, contributing to improved product quality.

d. Faster Deviation Management

CM facilitates real-time quality assurance, allowing manufacturers to identify and respond to anomalies quickly, reducing waste and rework.

e. Integration of Quality by Design (QbD)

Continuous manufacturing supports QbD by allowing enhanced process understanding and control throughout the product lifecycle.

Table 2: Assessment Metrics of Quality Improvement

Quality Metric	Traditional Batch	Continuous Manufacturing
Product uniformity	Moderate	High
Process control	Manual/semi-automated	Fully automated
Batch-to-batch variability	Common	Rare
Risk of cross-contamination	Higher	Lower
Waste and rework	Higher	Reduced
Time for deviation detection	Delayed	Real-time

Involvement of PAT in CM:

PAT is a system for designing, analysing, and controlling manufacturing through timely measurements (i.e., during processing) of quality attributes of raw and in-process materials and process conditions, with the goal of ensuring final product quality [16]. Due to the absence of isolated intermediates and the typically faster process dynamics for a continuous process that may necessitate more frequent measurements, real-time monitoring of process parameters and quality attributes of in-process materials typically constitutes an essential component of a control strategy for the establishment of a state of control. In addition to supporting the validation and control of the manufacturing process, PAT tools and principles can be used to gain process understanding. Multivariate models are often used for extracting process knowledge (e.g., blend uniformity) from the data provided by process analysers (e.g., spectroscopic measurements). Consensus standards are available for building, validating, and maintaining such multivariate models [17–19]. The sampling interface for continuous manufacturing systems can be challenging. Industrial experience indicates that poor measurement performance is often attributable to sampling system issues rather than the process analyser itself [20]. Online and in-line measurements may reduce but do not necessarily eliminate sampling errors. Thus, sampling considerations should be assessed. For example, the location of the sensor should be evaluated to achieve representative sampling and minimize the effect of the probe on the process. Powders and dispersions limit the penetration depth of spectroscopic techniques. This may increase the importance of the sample probe location [21], size of the sampling spot, intensity of the incident signal, etc. The sample size for the measurement should be representative of a unit dose and consider factors such as flow rate, penetration depth, and the number of scans. It is important to utilize the knowledge of the process dynamics (e.g., RTD) for determining the adequate sampling frequency for PAT measurements. The measurement frequency implemented should provide sufficient resolution for the detection of a pulse of variability from a process disturbance. The utilization of PAT tools can be applied to measuring surrogates for the quality attributes of a final product, some of which may have already been incorporated into the control strategy for process monitoring and control. For this reason, continuous manufacturing naturally lends itself to real-time release testing (RTRT), which is the ability to evaluate and ensure the quality of in-process materials and/or the final product based on process data that typically include a valid combination of measured raw material attributes and process controls [22]. A supervisory control and data

acquisition (SCADA) system can be implemented that incorporates measurements of process parameters, incoming raw material, and in-process material attributes, as well as final product quality attributes with a model of the process dynamics to reconcile the data in order to support RTRT [23,24]. Due to a high frequency of data collection, statistical methods for large sample sizes can be applied to increase the confidence level that the batch conforms to the desired quality. RTRT batch calculations should consider the observed variance in critical quality attributes over the production run to account for intra-batch variability. A risk analysis aids in consideration of PAT failure, and procedures can be developed in order to establish contingencies for process monitoring and batch release. The procedures could include end-product testing or utilizing surrogate measurements to ensure that the product maintains an acceptable level of quality. In addition to naturally lending itself to RTRT, the increase in the amount of process and quality data collected during continuous production facilitates the adoption of multivariate process monitoring approaches. Multivariate statistical process control (MSPC) is a process monitoring approach used to determine whether the variability in the process is stable over time. It can be used to detect abnormal events in the process that may lead to adverse consequences (e.g., out-of-specification product, equipment malfunction, or process safety incident) if not mitigated and provide diagnostic information about which process variables may be responsible for the event. Taking advantage of the fact that process variables are often correlated, MSPC simplifies process monitoring by reducing the number of control charts being tracked without losing information. MSPC may also enhance the detection of abnormal process operations by identifying changes in the relationships among process parameters and quality attributes [25] that may be difficult to detect using solely univariate process monitoring approaches.

Use Of Software To Conversion Of Traditional Batch Manufacturing To Continuous Batch Manufacturing: [11,26,27]

Software Name	Purpose	Function	Example
PAT Software	Monitors Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) in real time.	Inline, online, or at-line measurements Spectroscopy (NIR, Raman), chemometric modelling	Siemens SIPAT ABB PATVision Mettler Toledo iC
Manufacturing Execution Systems (MES)	Connects real-time plant-floor activities with higher-level business systems.	Batch record automation Electronic documentation Workflow and recipe management	Werum PAS-X Rockwell PharmaSuite Siemens Opcenter Execution Pharma

Distributed Control Systems (DCS) and SCADA	Control and monitor automated processes across multiple units in real-time.	Real-time data collection and feedback loops Process safety, alarms, trends	Emerson DeltaV Honeywell Experion PKS GE Digital iFIX
Modelling and Simulation Software	Simulates CM processes before implementation to optimize system design.	Material flow modelling Scale-up prediction Sensitivity analysis	gPROMS FormulatedProducts (Siemens PSE) Aspen Plus MATLAB Simulink
Quality by Design (QbD) Tools	Incorporates QbD principles into the CM design to ensure consistent quality.	Design space optimization Risk assessment	MODDE (Sartorius) Design Expert (Stat-Ease)

Conclusion:

The shift towards Continuous Manufacturing (CM) represents a significant change in pharmaceutical production, enhancing product quality, operational efficiency, and regulatory compliance. By incorporating Process Analytical Technology (PAT) tools, real-time monitoring, and advanced software systems, CM enables better control over critical quality attributes and reduces variability between batches. The use of digital technologies such as SCADA (Supervisory Control and Data Acquisition), MES (Manufacturing Execution Systems), and modelling software ensures a smooth transition from traditional batch methods. This transition provides improved scalability, reduces waste, and accelerates product release timelines. Additionally, CM naturally supports Quality by Design and real-time release testing frameworks, creating a strong foundation for personalized and decentralized manufacturing. As regulatory agencies increasingly endorse CM, it is on track to become the gold standard for quality-focused drug manufacturing in the pharmaceutical industry.

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