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# Process Analytical Technology for continuous manufacturing of solid-dosage forms

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ABSTRACT

Currently, pharmaceutical production is making the switch from batch processing towards continuous processing. The quality of intermediate and end products produced by batch processes is assured by off-line testing. It is obvious that off-line tests in analytical laboratories cancel out the advantages of continuous processing, so the critical quality attributes of continuously produced pharmaceuticals need to be monitored in real time. In 2004, the US Food and Drug Administration launched the process analytical technology (PAT) concept to stimulate the pharmaceutical industry to change from off-line to real-time quality testing. This review explores the implementation of PAT tools within continuous pharmaceutical processes (i.e., blending, spray drying, roller compaction, twin-screw granulation and compression), focusing on both opportunities and challenges.



**Contents**



## 1. Introduction

Pharmaceutical manufacturers of conventional solid-dosage forms (i.e., capsules and tablets) are interested to switch from batch processing towards continuous processing [1]. Continuous processing is characterized by

(i) integration of all unit operations; and,
(ii) the "one in, one out" principle.

Starting materials are continuously fed into the process, whilst end products are continuously removed at the same speed [2]. Several processing steps, currently used in batch manufacturing, are continuous, such as:

*Abbreviations:* API, Active pharmaceutical ingredient; CQA, Critical quality attribute; EMEA, European Medicines Agency; FBRM, Focused beam reflectance measurement; FDA, Food and Drug Administration; HPLC, High-performance liquid chromatography; KF, Karl Fischer; LIF, Light-induced fluorescence; MBSD, Moving block standard deviation; NIR, Near infrared; PAT, Process analytical technology; PC, Principal component; PCA, Principal-component analysis; PLS, Partial least squares; QbD, Quality by Design; R&D, Research and development; RSD, Residual standard deviation; UV, Ultraviolet.

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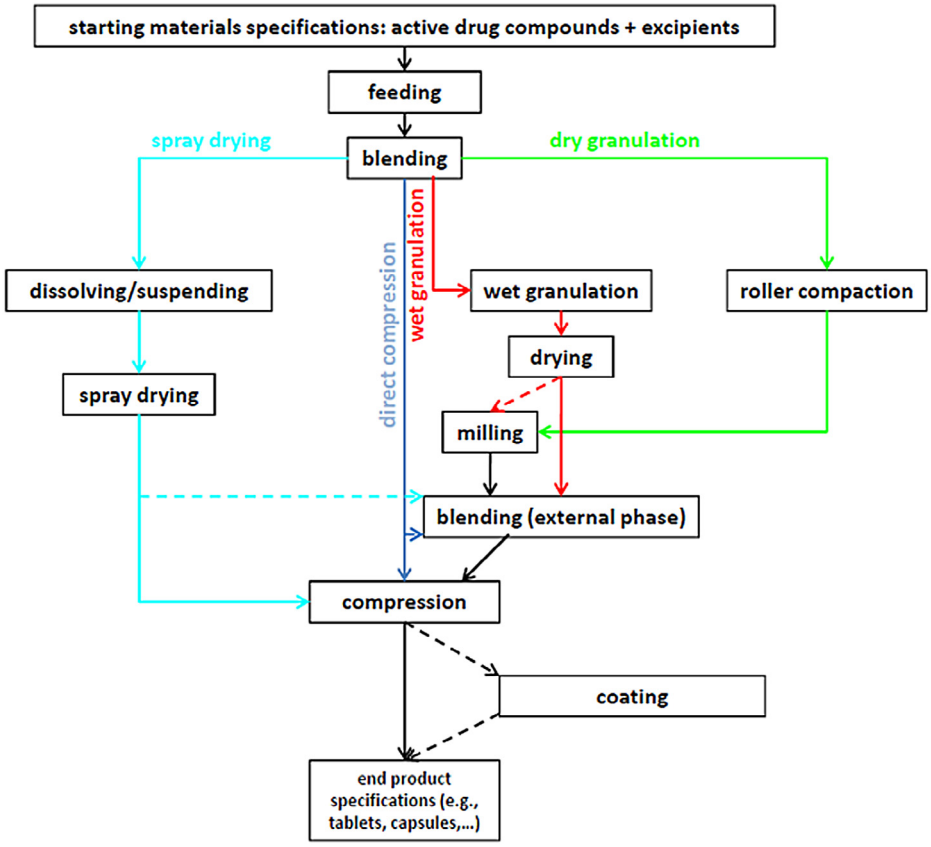


**Fig. 1.** Industrial processes most used for the production of pharmaceutical solid-dosage forms.

(i) feeding;
(ii) milling;
(iii) roller compaction, which is a dry granulation technique;
(iv) compression, where a blend of the active pharmaceutical ingredient (API) and excipients is compressed into tablets; and,
(v) spray-drying, in which a liquid is atomized into drops and then dried in a hot air flow (Fig. 1).

Furthermore, in the past decade, several companies have developed integrated powder-to-tablet production lines [2]. It is obvious that, for continuous processing, real-time quality control is indispensable, so the need to invest in process analytical technology (PAT) is strengthened. With the Horizon 2020 framework program for research and innovation in mind, the European Federation for Pharmaceutical Sciences (EUFEPS) also highlighted the need for appropriate in-line measurements, in order to make lean continuous manufacturing possible [3]. This review aims at summarizing the status of the implementation and the suitability of PAT tools for continuous pharmaceutical manufacturing processes of conventional solid-dosage forms, focusing on opportunities and shortcomings. Saerens et al. [4] earlier provided an overview of PAT monitoring in continuous hot-melt extrusion.

The adoption of continuous manufacturing of solid-dosage forms brings several advantages, but also challenges (Table 1). The advantages have their impact in three fields:

(i) product development and quality;
(ii) costs; and,
(iii) footprint.

Continuous production equipment implies fewer scale-up issues, since the size of the production lot is defined by the factor “time”, so the same equipment size can be used for development and pilot studies, clinical trials and full commercial production. Since time-intensive scale-up experiments are not needed, the development time is significantly decreased and the product can be launched faster to the market. It is important to mention that, especially now with scarcely filled pipelines, a shorter development time implies a longer monopoly for the company prior to patent expiry – which is a major economic advantage.

**Table 1**
Advantages and challenges for the adoption of continuous processing in the pharmaceutical industry

| Advantages | Challenges |
|---|---|
| No scale-up issues | Not appropriate for small product loads |
| Ease of automation | Less flexible regarding successive process steps |
| Production of desired product amount | Need for fast steady state |
| Better product quality assurance | Need for robust processes |
| Shorter product development time | No obvious batch definition |
| Shorter time-to-market | Production changes for already licensed products |
| Just-in-time-production | Regulatory uncertainty |
| Reduced capital investment | New mind-set needed for quality assurance (based on continuous in-process measurements) |
| Reduction of labor costs | |
| No transfer of intermediate products | |
| No storage of intermediate products | |
| Less floor space required | |
| Less energy consumption | |
| Less waste | |