Strategic Optimization of Sampling Points in API Tablet Coating

Author: Emmanuel Cintrón
Advisor: Miriam Pabón, Ph.D.
Graduate Project EXPO, May 2025

Abstract

This project explores optimizing the tablet coating process by shifting in-process sampling from late-stage (60–80%) to earlier stages (40–60%) to reduce equipment downtime caused by HPLC analysis delays. Using real production data and rigorous statistical tools (paired t-tests, Pearson correlation, Fisher's Z-tests, and F-tests), the study demonstrated that early sampling provides equivalent predictive accuracy while improving operational efficiency. Results include reduced downtime (up to 2.64 hours per batch), increased capacity (~13 million tablets annually), and significant cost savings. This data-driven approach supports lean manufacturing principles and regulatory compliance, offering a scalable solution to enhance throughput in pharmaceutical contract manufacturing.

Introduction

The tablet coating stage plays a vital role in ensuring product quality, uniformity, and API protection in solid oral dosage manufacturing. However, delays caused by in-process testing, particularly when relying on late-stage sampling and HPLC analysis, significantly impact equipment availability and production throughput. In contract manufacturing settings, where operational efficiency directly affects cost and client satisfaction, there is a clear need for data-driven improvements that support lean manufacturing and compliance.

Background

Sampling strategies are critical to maintaining control during the coating process, yet many are based on historical or operational convenience rather than statistical evaluation [1]. Literature highlights that strategic, representative sampling enhances endpoint prediction and reduces process variability [2], [3]. While HPLC remains the gold standard for assay accuracy [4], its time-intensive nature often introduces bottlenecks. Alternative tools like NIR and Raman spectroscopy offer promise but require extensive validation and are not universally applicable [5]. Recent advances in predictive modeling and Process Analytical Technology (PAT) enable earlier detection of coating endpoints, aligning with Quality by Design (QbD) and regulatory expectations [6].

Problem

Currently, three in-process samples are collected at 60%, 70%, and 80% of the calculated coating endpoint and analyzed via HPLC, resulting in approximately three hours of production hold time per batch. This delay hinders equipment availability and reduces manufacturing efficiency. This project evaluates whether shifting sampling to 40%, 50%, and 60% can reduce downtime while maintaining endpoint prediction accuracy. To ensure robustness, additional sampling scenarios—such as full five-point models and variations excluding the 60% point—were analyzed. This initiative seeks to enhance flow, reduce deviations, and strengthen cost-efficiency through improved equipment absorption and throughput.

Methodology

This project applies the DMAIC methodology (Define, Measure, Analyze, Improve, Control), widely used in process improvement, to optimize the in-process sampling strategy in tablet coating.

Define

The current approach uses three sampling points (60%, 70%, 80%)—a simplification from the original five-point method. NIR once mitigated HPLC delays, but its limited current use has reinstated significant hold times. The objective is to assess whether sampling earlier (40%, 50%, 60%) can reduce downtime while maintaining endpoint prediction accuracy and product quality.

Measure

Fourteen commercial batches were sampled at five coating volumes: 40%, 50%, 60%, 70%, and 80%. All samples were analyzed via HPLC and entered into a validated prediction tool to estimate the endpoint based on volume and %API. This dataset enabled a reliable comparison of alternative sampling strategies.

Analyze

Five sampling scenarios were constructed and compared to the reference model (Scenario C, using all five sampling points:

- **Scenario A:** Early sampling points – 40%, 50%, and 60%
- **Scenario B:** Current sampling approach, late sampling points – 60%, 70%, and 80%
- **Scenario C:** Reference Model, all five sampling points – 40%, 50%, 60%, 70%, and 80%
- **Scenario D:** Reduced early sampling points – 40% and 50%
- **Scenario E:** Reduced late sampling points – 70% and 80%

Each scenario's endpoint predictions were statistically compared to the reference using metrics such as mean prediction difference, standard deviation, confidence intervals, and inferential tests (paired t-test, Pearson correlation, Fisher's Z, and F-test). The analysis evaluated whether earlier or reduced sampling could maintain alignment with the five-point model and whether the 60% sample was critical to predictive stability.

Improve

Scenario A showed strong statistical alignment with the reference model. Implementation could reduce process hold time, improve equipment availability, and enhance cost-efficiency. These gains are supported by quantitative data and meet regulatory expectations.

Control

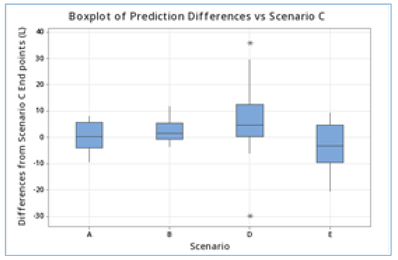
If adopted, the revised sampling approach would be formalized through updates to SOPs, batch record templates, and quality agreements. A monitoring plan would sustain predictive reliability, ensuring consistency across future batches, product strengths, and manufacturing conditions.

Results and Discussion

A comprehensive analysis was conducted across 14 commercial batches using HPLC results and a validated endpoint prediction model. Scenario A consistently demonstrated superior performance in both statistical alignment and operational efficiency compared to the current strategy.

Graphical evaluations—including boxplots, scatterplots, bar charts, and time series plots—were used to assess prediction bias, variability, and correlation with the reference model.

Figure 1
Boxplot of Prediction Differences from Scenario C for All Sampling Strategies



Scenario A exhibited minimal bias, a narrow interquartile range, and no outliers, indicating high consistency. In contrast, Scenario B showed a slight positive bias, while Scenarios D and E revealed greater dispersion and reduced reliability.

Statistical tests further validated these observations:

- **Paired t-test:** Scenario A ($p = 0.854$) showed no significant deviation from the reference model; Scenario B ($p = 0.040$) indicated consistent overprediction.
- **Fisher's Z-test:** No significant correlation difference between A ($r = 0.868$) and B ($r = 0.937$); $p = 0.365$.
- **F-test:** No significant difference in variability between A and B ($p = 0.947$).

Operationally, Scenario A reduced coating downtime by up to 2.64 hours per batch, enabling a projected gain of ~13.4 million tablets/year and improved absorption (~$2.2 million/year). Estimated savings include ~$60,000 annually in overtime and reduced deviation risk. By enabling earlier detection and decreasing reliance on automation prompts, this strategy aligns with QbD principles and supports robust, compliant process control.

Table 1
Comparative of Scenario A and Scenario B Across Key Performance and Operational Metrics

Category	Scenario A (40–60%)	Scenario B (60–80%)
Prediction Bias	Minimal (0.30 L)	Significant overprediction (2.60 L)
Correlation (to Ref.)	Strong (r = 0.868) – statistically equivalent	Slightly stronger (r = 0.937)
Variability	Comparable – Not significantly different	Slightly lower – Not significantly different
Downtime	Reduced by up to 2.64 hrs/lot	Longer retention time
Capacity Impact	~13.4M additional tablets/year	None
Absorption Gains	~$2.2MM/year	None
Overtime Impact	Potential reduction of +$60,000/year	Current average: 190 hrs/month
Deviation Risk	Reduced – earlier detection posible	Actual risk – late sampling delayed response

Conclusions

Scenario A (40–60%) proved to be a statistically robust and operationally efficient sampling strategy for API tablet coating. It demonstrated minimal prediction bias (0.30 L), strong alignment with the reference model ($p = 0.854$), and no significant difference in correlation or variability. Operational gains included reduced downtime (up to 2.64 hrs./lot), increased capacity (~13.4M tablets/year), improved absorption (~$2.2 million/year), and over $60K/year in overtime savings.

Additionally, early sampling enhanced predictive control, supporting QbD principles and minimizing deviation risks. The strategy offers a scalable improvement aligned with regulatory expectations and continuous improvement goals, positioning Scenario A as the recommended model for implementation.

Future Work

Building on the results of this project, the following actions will be pursued to expand and strengthen the implementation of early sampling strategies:

- Extend validation to the 50/500 mg presentation.
- Deploy real-time tracking to confirm long-term robustness of predictions.
- Evaluate integration of non-destructive endpoint tools (e.g., NIR).
- Assess scalability across additional coating processes and product strengths.

Acknowledgements

Special thanks to Dr. Miriam Pabón González for her guidance and continuous support throughout this project. I also acknowledge Dr. Rafael Nieves for his valuable assistance during the initial phase of the research. Appreciation is extended to César Rodríguez, Director of Operations, for assigning and supporting this initiative. This work was completed as part of the Master of Engineering in Manufacturing Engineering program at Polytechnic University of Puerto Rico.

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