# Engineering Considerations on Modeling for Pharmaceutical Process Analytical Technology (PAT) Applications

*Huiquan Wu[1*], Meiyu Shen[2], Thomas D. Wheelock[3], Mansoor A. Khan[1]*
*[1]Division of Product Quality Research (DPQR, HFD-940), OTR/OPS/CDER/FDA, Silver Spring, MD*
*[2]Office of Biostatistics, CDER, FDA, Silver Spring, MD*
*[3]Chemical and Biological Engineering Department, Iowa State University, Ames, IA*
[*] Corresponding author: 301-796-0022(Tel); 301-796-9816 (Fax); huiquan.wu@fda.hhs.gov (Email)

## Introduction

Recent FDA presentations and media reports indicate that process understanding is critical to enhance manufacturing efficiency and reduce the likelihood of producing products of poor quality [1]. The FDA's Process Analytical Technology (PAT) Guidance [2] also highlights the importance of process understanding and process control. Focusing on pharmaceutical manufacturing processes may open up unprecedented opportunities and challenges for engineering disciplines, such as applying fundamental engineering principles to process/product design, process scale-up, process monitoring, and process control. Process modeling as an enabling tool for linking various stages in the manufacturing pipeline will play a key role during the implementation of PAT in pharmaceutical development, manufacturing, and quality assurance, and is also being reflected in recent ICH (International Conference on Harmonization) Guidelines Q8 [3] and Q9 [4]. Although other industry sectors have been adopting various process control tools as an essential measure for achieving and ensuring Quality-by-Design for many years, using engineering modeling as the foundation for process control remains a significant challenge for the pharmaceutical industry. In this regard, specific case studies can be very helpful as they may not only have a positive impact on the pharmaceutical practitioners, they may also convince the pharmaceutical community to embrace engineering principles and practices. These practices have proven extremely valuable in the process development, scale-up, and manufacturing domain.

In this work, two case studies are presented to illustrate how engineering principles and modeling tools can be utilized to enhance pharmaceutical process understanding and to help achieve Quality-by-Design from the product/process design perspective.

## Case Study of Multivariate Modeling of a Tablet Dissolution Process

Near-infrared (NIR) spectroscopy is a fast and reliable analytical technique which has been adopted for many successful applications in other industry sectors such as agricultural processing, petrochemical refining, wine making, and food processing over the last 30 years. It has gained increasing popularity in the pharmaceutical industry over the last decade after FDA officially approved the first NIR-based analytical method in early 1990s. Over the past few years, it has gained

more momentum from the FDA's Process Analytical Technology (PAT) Initiative and the FDA's PAT Guidance as a fast and convenient process analyzer. It has been used for raw material identification, process monitoring, tablet quality control (QC), etc. In this regard, chemometric techniques in general, and multivariate statistical data analysis in particular, have played a significant role during the initial stage of introduction of PAT into the pharmaceutical community. However, the integration of engineering modeling practice into this emerging exciting area to provide,a robust model which carries rich information and knowledge of both product and process, has been an area to be researched. In the authors' opinion, it presents a great challenge to the chemo-metrics modeling community.

This case study deals with the multivariate modeling of a tablet dissolution process. In conjunction with the multivariate statistical modeling, classical engineering principles of mass transfer and Fick's diffusion law were applied successfully to accomplish two goals: modeling the tablet dissolution process and identifying critical process variables for this process, as discussed below.

1. Experimental tablet formulation and processing variables

Experimental tablets containing theophylline (API), lactose, Avicel PH-101, and magnesium stearate were made at a contract manufacturing site by direct compression first (with hardness *ca*. 12 kilopounds) and then coated with a mixture of Surelease and HPMC. The coating levels were varied between 1% and 17% weight gain. The tablet core formulations are listed in the Table 1.

**Table 1**. Controlled-release tablet core formulations

| Theophylline (mg) | Fast Flo Lactose (mg) | Avicel PH-101(mg) | Mg Stearate (mg) | Total (mg) |
|---|---|---|---|---|
| 80 | 187 | 60 | 3 | 330 |
| 90 | 177 | 60 | 3 | 330 |
| 100 | 167 | 60 | 3 | 330 |
| 110 | 157 | 60 | 3 | 330 |
| 120 | 147 | 60 | 3 | 330 |

2. NIR characterization and dissolution testing

All coated tablets were scanned by a FOSS NIR Spectrometer. NIR spectra were recorded. Then dissolution tests were conducted with all of these coated tablets using a USP II standard method. Dissolution profiles were obtained.

3. Multivariate modeling

Principal Component Analysis (PCA) was performed on the NIR spectra. Principal Component Regression (PCR) and Partial Least Squares (PLS) were used to correlate the NIR spectra with the dissolution data.

4. Engineering modeling

The initial dissolution rates of the coated tablets were calculated from the tablets' dissolution profiles. The initial dissolution rates of coated tablets were then plotted against the coating levels of the tablets. From the results of the PCA

conducted in the Multivariate modeling, a plot of the score values of the first principal component (PC) vs. coating levels of the tablets was made. By comparison, it was observed that a similar trend was displayed on these two types of plots: there is an approximate linear relationship between the *y*-axis (either the initial dissolution rate or the score value of the 1st PC) and the *x*-axis (the coating level). This fact suggests the 1st PC characterizes the variability of coating level. On the other hand, various dissolution models with different kinetic orders were used to fit the dissolution profiles. The results show that Fick's Diffusion Law is able to describe elegantly the initial dissolution behaviors of the coated tablets. This collective evidence shows that the initial dissolution rate of the coated tablets is inversely proportional to the thickness of the coating layer. Research related to the lag time in the original dissolution profiles has been underway.

5. Critical variable identification

In this case, if we take the dissolution rate of coated tablet as a clinical surrogate, then through modeling and analysis, the coating layer thickness or coating level is the critical variable. This conclusion is based on the fact that both the tablet formulation and process information (including the dissolution process) have been taken into account; therefore the identification of coating level as a critical variable has more practical significance. For example, we have to control the coating weight gain during the coating operation precisely, such that a pre-defined release profile for the controlled-release dosage form can be achieved in the in vitro study, and subsequently a pre-defined bioavailability and efficacy of the controlled-release dosage form can be achieved.

## Case Study on Scale-up of a Multi-phase Agglomeration Mixing System

1. Challenges and relevance of engineering scale-up for PAT implementation in pharmaceutical industry

Scale-up of a multi-phase mixing system has proven to be a very challenging task for the engineering community, due to a number of reasons including (a) the complexity of the hydrodynamics; (b) the impact of the size, type, and geometric design of the system on the hydrodynamics which are generally not well-understood; and (c) the coupling effects between mass transfer, momentum transfer, and hydrodynamics within the system. Therefore, engineering scale-up methodology remains a great challenge and has been an active research area over several decades.

According to the FDA PAT Guidance, "The Agency considers PAT to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality." Today's reality is, when designing a pharmaceutical process for manufacturing, typically the procedure is based on results of lab-scale and some small-scale pilot plant work, technology transfer, and process validation. Unfortunately, no strict engineering scale-up method has been widely adopted, at least according to available public literature. However, to design an elegant PAT system and make it work at an acceptable engineering level in the pharmaceutical

industry, in authors' view, requires a detailed scale-up study [5]. In this regard, the relevance of chemical engineering scale-up methodologies to pharmaceutical processing and quality-by-design is easily appreciated.

2. Scale-up study of a multi-phase mixing and agglomeration system

This case study is based on the scale-up of a multi-phase selective agglomeration mixing system. It illustrates how chemical engineering scale-up methodologies can be utilized to cope with the scale-up of a mixing and agglomeration system. In this case, there were two types of solid particles, two immiscible liquid phases (oil and water), and a gas phase in the form of gas bubbles. The experiments involving mixing and selective agglomeration were carried out in a facility of the Iowa State University Center for Sustainable Environmental Technologies, with systems of different sizes [6]. The effects of various process conditions (such as impeller tip speed, concentrations of oil, air, and solids) on mixing and selective agglomeration were determined. The minimum time required to produce spherical agglomerates, $t_E$ , and the final size of the agglomerates, $d_p$, as measured by an off-line imaging system, were analyzed by applying a combination of multiple linear regression analysis and statistical analysis of variance (ANOVA) to determine the dependence of $t_E$ and $d_p$ on the independent variables. Correlations were established to describe how processing parameters, such as power input per unit volume (P/V) and impeller tip speed (S), impact the process outcomes represented by $t_E$ and $d_p$. By selecting a suitable scale-up rule, the mixing system was scaled-up successfully by utilizing three systems of increasing size corresponding to tank diameters of 11.4, 15.2, and 24.0 cm [7].

## Challenges and Opportunities for Developing Engineering Modeling of PAT

The realities of pharmaceutical process development can be characterized by a high attrition rate and few successful campaigns. Typically among 30~50 candidates entering early toxicology testing and Phase I trial stage, only 1~3 candidates make it to Phase III trial and NDA filing. Although safety and efficacy are often thought of as primary reasons for droping a candidate, product quality and CMC (chemistry, manufacturing, and control) issues are another important reason. The latter may arise from a lack of both an integrated team approach and an early engineering input. Because the pharmaceutical research and development has been traditionally more focused on the chemistry side, with little or limited engineering input. The limitation of this traditional practice has been discussed in the public domain over the last few years. For a candidate to survive through various development stages including Phase I/II/III, scale-up, and commercial manufacturing, a well-integrated, cross-discipline team approach is essential. In this regard, integration of engineering principles and practices into pharmaceutical research and development, scale-up, and manufacturing would provide many benefits [5]. Engineering modeling as a critical means for implementing PAT in the pharmaceutical industry can play a key role in realizing these benefits.

However, modeling results are only as good as the weakest link in the modeling chain which includes: experimental design (problem statement and measurement strategy, design), data collection (measurement), and data analysis and modeling

(analysis and control). These echo well the three basic components highlighted in the FDA PAT Guidance: design, analysis, and control. Obviously, it is extremely important to select the right tools to address modeling issues from the beginning. In the mean while, it is equally important to make an effort to link various development stages together, from an integrated and systems approach. For a particular PAT project, depending on the experimental design protocol and resources available including engineers and scientists, process analyzers, measurement interfaces, product/process characterization tools, data analysis software, process integration and control tools, there are various strategies which can be used to address the modeling issues. These strategies include but are not limited to the following:

(1) first principle approach [8]
(2) mechanism-based approach [9]
(3) multivariate modeling approach (needs to bring the process/product knowledge into the PAT modeling area) [10]
(4) scale-up methodology study [7] or using continuous processing mode to bypass process scale-up challenges [11]
(5) system integration approach for closed-loop process control [12]
(6) model linkage approach to bridge gaps among various modeling methodologies [13]

Items (1) to (6) actually echo well a famous philosophy that guides us to gain and enrich our understanding of a particular subject: theoretical—empirical—practical--theoretical. If our understanding of pharmaceutical processes and unit operations reaches such a stage that we are able to (a) describe and explain any pharmaceutical process or unit operation in precise physical and mathematical language; and (b) predict process outcomes and product quality attributes precisely, the merits of engineering modeling Quality-by-Design (QbD) could be fully realized. However, to achieve engineering modeling QbD, in the authors' opinion, the following aspects are critical:

(1) gaining a comprehensive knowledge of products/processes and computational skills;
(2) initiating and maintaining significant collaborative efforts among scientists and engineers across disciplines;
(3) collectively addressing technical challenges within the process modeling and control community to meet emerging needs for PAT implementation.

Each one of these presents a great challenge and an opportunity for the engineering modeling community during implementation of PAT in the pharmaceutical industry.

## Conclusions

In this work, two case studies which focus on processes are presented to illustrate how engineering principles and modeling tools can be integrated to enhance pharmaceutical process understanding and to help achieve Quality-by-Design from the product/process design perspective. Challenges and opportunities

for application of engineering modeling to PAT are discussed briefly, from an engineering modeling QbD perspective.

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## Disclaimer

*The views and opinions expressed in this paper are only of authors, and do not necessarily reflect the views or policies of the FDA.*

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