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RESEARCH ARTICLE

Optimization of the Manufacturing Process for Oral Formulations Using Multivariate Statistical Methods

Tadashi Norioka · Shingo Kikuchi · Yoshinori Onuki · Kozo Takayama · Keiji Imai

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Abstract Multivariate statistical analysis has and will continue to play an important role in the development of pharmaceutical products. Although many examples have been reported, few have applied multivariate statistical analysis to the overall manufacturing process. In this study, the model drug core tablets were manufactured under different conditions, and the challenge to understand the cause-and-effect relationship between process parameters and response variables was addressed by applying three different multivariate statistical methods. It was confirmed that conventional multivariate statistical methods were able to extract the process parameters (granulation time, drying temperature, blending time, and compression force) that affected both the average and the variance of the response variables (hardness, content uniformity, and dissolution) with a science-based rationale. In order to overcome the multiobjective optimization problem among the response variables, an advanced multivariate statistical method was also applied. It was confirmed that the mathematical models of response variables were determined with sufficiently high accuracy and the optimal levels of both process parameters and response variables were determined with high reliability, which provided a more profound understanding of the process. These methods enable us to develop pharmaceutical products more efficiently and accurately.

T. Norioka (✉) · S. Kikuchi · Y. Onuki · K. Takayama
Department of Pharmaceutics, Hoshi University,
2-4-41 Ebara,
Shinagawa-ku, Tokyo 142-8501, Japan
e-mail: tadashi.norioka@jp.astellas.com

T. Norioka · K. Imai
Pharmaceutical Technology and Research Laboratories,
Astellas Pharma Inc.,
180 Ozumi,
Yaizu, Shizuoka 425-0072, Japan

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Introduction

In the later development phase of pharmaceutical products, once the formulation of the drug has been determined, the main issue is the optimization of the manufacturing process to develop a robust and stable commercial manufacturing process. Historically, the optimization of the manufacturing process has mostly involved univariate methods where the effects of a single variable are examined for a small number of conditions; for example, a value of the first variable is selected and kept constant as a second variable is examined. However, the univariate method does not consider the effects of interactions between multiple variables. As a result, even if the optimal value for a single variable can be determined, the optimal values for multiple variables, which are not necessarily the same, are not. In recent years, the pharmaceutical industry has focused substantial effort on improving its understanding of key unit operations and on developing statistical, instrumental, and fundamental methods for characterizing and controlling the sources of variability in product performance. The "process understanding" that is considered a keystone of the quality-by-design initiatives allows the development of a robust and stable manufacturing process with a science-based rationale. For these reasons, the pharmaceutical industry is transitioning from univariate methods to multivariate statistical methods. Although many examples applying multivariate statistical methods have been reported [1–3], few apply multivariate statistical methods to the overall manufacturing process of pharmaceutical products, a sequence of multiple unit operations. In this study, optimization of the overall manufacturing process was attempted by applying three different multivariate