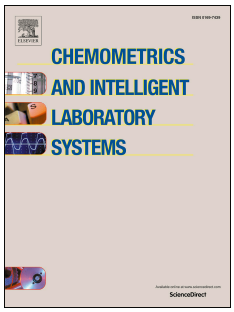
Accepted Manuscript



Optimal design of experiments for excipient compatibility studies

Wannes G.M. Akkermans, Hans Coppenolle, Peter Goos

PII: S0169-7439(17)30017-5

DOI: 10.1016/j.chemolab.2017.09.012

Reference: CHEMOM 3500

To appear in: *Chemometrics and Intelligent Laboratory Systems*

Received Date: 10 January 2017

Revised Date: 17 September 2017

Accepted Date: 19 September 2017

Please cite this article as: W.G.M. Akkermans, H. Coppenolle, P. Goos, Optimal design of experiments for excipient compatibility studies, *Chemometrics and Intelligent Laboratory Systems* (2017), doi: 10.1016/j.chemolab.2017.09.012.

Optimal design of experiments for excipient compatibility studies

Wannes G.M. Akkermans
Faculty of Bioscience Engineering
KU Leuven

Hans Coppenolle
Statistics and Decision Sciences
Janssen Pharmaceutica

Peter Goos
Faculty of Bioscience Engineering
KU Leuven, and
Faculty of Applied Economics
Universiteit Antwerpen

Abstract

A crucial stage in the development of medical drugs is to study which additives, usually called excipients, impact the active ingredient stability. This type of study is generally named an excipient compatibility study and requires a mixture experiment. Subsequently, the effect of the storage conditions, more specifically the relative humidity and temperature, on the stability is investigated. This so-called accelerated life test involves a factorial type of experiment. It has become, however, customary to include the storage conditions in the compatibility study. This provides valuable information concerning potential interactions between excipient combinations and storage conditions. Experiments that combine a mixture experiment with a factorial experiment are generally named mixture-process variable experiments. A limited number of designs for mixture process-variable experiments are available in the literature. One problem is that the proposed designs offer little flexibility. Another is that the required number of runs becomes prohibitively large for large numbers of mixture components. In this paper, we examine flexible, optimal designs for realistic mixture-process variable experiments. Our motivation is to provide guidance to pharmaceutical formulation scientists concerning state-of-the art models and designs for excipient compatibility studies. Using several proof-of-concept examples, we demonstrate that I-optimal designs offer both flexibility and small variances of prediction. We also discuss a real-life example, which could be used as a blueprint for future studies. Because many excipient compatibility studies are not completely randomized, we pay special attention to their logistics and to the resulting randomization restrictions, which lead to split-plot