

Designed Blending for Near Infrared Calibration

OTTO SCHEIBELHOFFER,^{1,2} BIANCA GRABNER,¹ ROBERT W. BONDI JR.,³ BENOÎT IGNE,³ STEPHAN SACHER,¹ JOHANNES G. KHINAST^{1,2}

¹Research Center Pharmaceutical Engineering GmbH, Graz, Austria

²Institute of Process and Particle Engineering, University of Technology, Graz, Austria

³GlaxoSmithKline, King of Prussia, Pennsylvania

Received 6 February 2015; revised 20 March 2015; accepted 17 April 2015

Published online 15 May 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24488

ABSTRACT: Spectroscopic methods are increasingly used for monitoring pharmaceutical manufacturing unit operations that involve powder handling and processing. With that regard, chemometric models are required to interpret the obtained spectra. There are many ways to prepare artificial powder blend samples used in a chemometric model for predicting the chemical content. Basically, an infinite number of possible concentration levels exist in terms of the individual components. In our study, design of experiments for ternary mixtures was used to establish a suitable number of blend compositions that represents the entire mixture region of interest for a three component blend. Various experimental designs and their effect on the predictive power of a chemometric model for near infrared spectra were investigated. It was determined that a particular choice of experimental design could change the predictive power of a model, even with the same number of calibration experiments. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association *J Pharm Sci* 104:2312–2322, 2015

Keywords: near-infrared spectroscopy; partial least squares; factorial design; powder technology; pharmaceutical engineering

INTRODUCTION

Near-infrared spectroscopy (NIRS) is frequently used to quantify chemical substances. Especially in the pharmaceutical industry, NIRS has gained a strong foothold for process and product monitoring, as it is a contactless and rapid measurement method. A common application is to ensure correct composition and homogeneity after a blending process. Within the context of continuous manufacturing and real-time release, increased attention to NIRS is to be expected.^{1,2}

Quantification with NIRS is based on the measured specific material absorption (due to both chemical and textural features) in a sample. To relate quantity and absorbance, calibration is necessary. A widespread regression method used for this case is Partial Least Squares Regression (PLS).³

The problem of NIR calibration set design is associated with all quantitative models, and powder blend assay is a prominent example. The general rule is that all possible variance must be covered by the samples.⁴ As a result, all practically relevant concentration modifications and changes in raw material properties and environmental conditions (e.g., humidity) must be considered when preparing the samples.^{5–7} Moreover, achieving and maintaining robust model performance requires constantly maintaining and updating the calibration.^{8,9}

In the case of pharmaceutical blends, some degree of freedom exists with regard to designing a sample set for calibration. In principle, any concentration combination can be prepared. Typically, experience or convenience determine which concentration ratios are used. This involves deciding on the number of concentration levels, the concentration range to be covered, and the concentration increment in between the levels.

Here, we intend to provide a more rational approach. A discussion of the challenges and the resulting decisions for concentration level settings is presented for several cases in the following sections. Those are arranged by increasing complexity of the formulation (binary, ternary, and polyadic).

Binary Blends

According to the Beer–Lambert law, calibration should be straightforward: as the absorbance has a linear relationship with the concentration, two concentration levels are sufficient for performing a calibration. In reality, however, this is not true for several reasons.^{10,11} At different concentration levels, not only absorbance but also scattering behavior changes; physical sample differences, such as density and texture, alter the effective light path and matrix materials can quench radiation. This effects create a non-linear relationship between the concentration of the material of interest and measured absorbance.^{10,12} Nevertheless, for small changes in the concentration, the relationship is still approximately linear.^{10,13} In practice, the most common strategy is as follows:

Samples are prepared roughly in a range around the target concentration, which is split into multiple levels.^{1,14} This way, the product's target concentration range is well within the calibration region and deviations can be found and modeled with sufficient accuracy. The ICH Guideline for Validation of Analytical Procedures recommends a concentration range of 80%–120% of the target level, and at least five concentrations steps to prove linearity.¹⁵ The new EMA guideline on NIR states that samples should be distributed evenly.⁴ However, as shown in Table 1, widely different methods are applied. Generally, several samples should be available per source of variance (concentration, humidity, season, etc.) without inferring how samples are distributed between the extreme values of the variation source.^{4,10}

As a non-linear relationship between absorbance and concentration will result in poor model performance, a model

Correspondence to: Johannes G. Khinast (Telephone: +43-316-873-30400; Fax: +43-316-873-30402; E-mail: khinast@tugraz.at)

Journal of Pharmaceutical Sciences, Vol. 104, 2312–2322 (2015)

© 2015 Wiley Periodicals, Inc. and the American Pharmacists Association

Table 1. Examples of Binary Powder Blend Calibrations for NIR

Range		Levels	Increment	Accuracy		Source
Absolute (%)	Relative (%target)			Absolute (%)	Relative (%target)	
3–11		3	4	0.5		16
<i>11.25–18.75</i>	75–125	3	<i>3.75</i>	<i>0.44</i>	2.95	17
1.2–5.4	25–125	5	<i>1.05</i>	0.2	4.7	18
10–90		9	10	5		19
0–15		10	1.5	0.41		20
20–30		10	1	0.57		21
0–100		11	10	2.97		22
45–55		12	2.5	0.8		21
40–60		13	2	2		22
0–100		15	5, 10	2.5		23
0–100		15	var.	3		24
0–100		18	5, 10			25
0–3	1	30	0.1	0.05	5	26,27

The concentration range is given in absolute percentage (w/w) of the blend and is relative to the target level of API. The number of concentration levels must not be the same as the number of samples (typically multiple). The increment from one level to the next is given by the percentage of the total blend. Accuracy (e.g., in the form of root mean square error of cross-validation) is given by the percentage of the total blend and relative to the concentration level. Values in italics are not stated directly in the sources but are extrapolated from context. This table only shows the variety of strategies that exist for model development and is not meant to provide an assessment of the models in terms of their accuracy since a lot more parameters may influence it.

covering a smaller concentration range will be more accurate. For that reason, it is strongly recommended to use two models: one for a coarse prediction of concentration as long as the variation is high and the other one to cover a small range around the target concentration for a precise and accurate prediction in the critical range. This technique is known as bracketing.¹⁰

Ternary Blends

For ternary blends, the number of possibilities in terms of the concentration levels increases further. Ternary blends can be described via fractions of their three components and the closure condition (i.e., the sum of all component fractions must be 1), which can be represented graphically in a mixture triangle, the so-called simplex. When using p levels per component, the number of concentration level combinations N , or distinct blend compositions, is given by

$$N = \sum_{k=0}^p p - k = \frac{1}{2}p(p + 1) \quad (1)$$

This results, for example, in 55 samples for 10 concentration levels and can easily be visualized in a mixture diagram, showing the concentration of all three components and the closure condition via a regular grid.^{28,29} There are several strategies for distributing the chosen concentration levels in the mixture simplex. In a ternary mixture, one component's concentration can be kept constant, whereas the other two vary. Thus, the concentration levels for one substance will appear multiple times. The issue in optimal sample selection is to reduce the number of samples in order to avoid performing all of the above experiments.

In the design of experiments (DoE) for mixtures, the relevant compositions distributed across the simplex are strategi-

cally chosen to model a target variable in an effective way. This defines a certain number of necessary blend compositions, that is, experimental runs. A target variable can be any property of interest, which should be quantitatively explained and predicted by knowing the blend composition (which constitutes the independent variables). A DoE is often a good starting point for determining the concentration levels for calibration.^{4,10,30,31} On the one hand, modeling a target variable by blend composition, and on the other hand, estimating the blend composition by measured spectra of the blend, share some common assumptions. In both applications, the relationship between the data sets is assumed to be appropriately approximated by a simple mathematical function. In most cases, a linear relationship is assumed, or variable transformations are used, to linearize the relationship. This agrees with the ICH Q2 recommendation.¹⁵

In chemometric model development using PLS, deviations from the linear behavior are circumvented by establishing several levels for the target variable and filtering the spectra for the parts that indeed have a linear behavior. As noise contained in the spectra does not have such behavior, it is excluded. Different spectral regions are combined to cancel out the influences of several components. With that regard, correlations between different component concentrations in preparing the calibration samples should be avoided, which is in line with the requirement to have independent factors in an experimental design.

If linear behavior is not observed, transformations of the spectra or, less frequently, of the target variables are performed. In the DoE, the target variables are frequently transformed to reach a linear relationship, and the measurement noise is estimated via repetition samples in a representative setting (mostly at center points). As such, DoE could be applied to choosing samples for a chemometric model.^{10,30,31} Note, however, that although in DoE, the concentrations are the factors (independent variables) and the spectra are the actual response (dependent variable), in a chemometric model, the spectra are the independent variables and the concentrations are the dependent (target) variables.

The literature does not recommend any particular mixture design for NIR calibrations: Shi et al.³² used the Plackett–Burman design, whereas Karande et al.³³ and Sekulic et al.³⁴ relied on the D -Optimal design. Wu et al.³⁵ employed the extreme vertices design. After testing five experimental designs and evaluating them based on their root-mean-square error of prediction values, Bondi et al.³⁶ reported that the I -Optimal Design provided the best results. The investigated designs were flat and involved two factors: the concentration of a substance and the ratio between two other substances.³⁶ This approach may lead to under- or over-representation of a certain mixture region (as can be visualized by a coordinate transformation) and bias the model toward certain concentration levels.

Polyadic Blends

Typically, pharmaceutical blends contain more than three substances. Mixture designs for more than three components are hard to grasp visually and often require computationally generated optimal designs. However, because not all components deserve equal attention, calibration for polyadic blends can often be simplified.

The most important component is the active pharmaceutical ingredient (API). Its concentration has to be carefully monitored and the calibration must be set up in most reliable

Download English Version:

<https://daneshyari.com/en/article/2484527>

Download Persian Version:

<https://daneshyari.com/article/2484527>

[Daneshyari.com](https://daneshyari.com)