Effects and Detection of Raw Material Variability on the Performance of Near-Infrared Calibration Models for Pharmaceutical Products

BENOIT IGNE,[1] ZHENQI SHI,[1,2] JAMES K. DRENNEN III,[1,2] CARL A. ANDERSON[1,2]

[1]Duquesne University Center for Pharmaceutical Technology, School of Pharmacy, Pittsburgh, Pennsylvania 15282
[2]Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, Pennsylvania 15282

Received 8 October 2013; revised 12 November 2013; accepted 21 November 2013

Published online 12 December 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23816

ABSTRACT: The impact of raw material variability on the prediction ability of a near-infrared calibration model was studied. Calibrations, developed from a quaternary mixture design comprising theophylline anhydrous, lactose monohydrate, microcrystalline cellulose, and soluble starch, were challenged by intentional variation of raw material properties. A design with two theophylline physical forms, three lactose particle sizes, and two starch manufacturers was created to test model robustness. Further challenges to the models were accomplished through environmental conditions. Along with full-spectrum partial least squares (PLS) modeling, variable selection by dynamic backward PLS and genetic algorithms was utilized in an effort to mitigate the effects of raw material variability. In addition to evaluating models based on their prediction statistics, prediction residuals were analyzed by analyses of variance and model diagnostics (Hotelling's T^2 and Q residuals). Full-spectrum models were significantly affected by lactose particle size. Models developed by selecting variables gave lower prediction errors and proved to be a good approach to limit the effect of changing raw material characteristics. Hotelling's T^2 and Q residuals provided valuable information that was not detectable when studying only prediction trends. Diagnostic statistics were demonstrated to be critical in the appropriate interpretation of the prediction of quality parameters. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:545–556, 2014

Keywords: near-infrared spectroscopy; raw material variability; variable selection; iterative PLS; dynamic backward iterative PLS; partial least squares; polymorph; particle size; excipients

INTRODUCTION

A near-infrared (NIR) calibration model should be developed with samples including most of, if not all, the variability that it will encounter during its use.[1,2] Although it is possible to include variability that is known or reasonably anticipated, it is often not convenient. First, it is impossible to foresee the state of the samples that are to come (next crop year, next batches). Second, it is highly impractical, as requiring large calibration data sets, possibly based on rigorous design of experiments, and could quickly become prohibitively expensive. In the absence of built-in robustness, samples presenting variability outside of the calibration set are predicted based on the extrapolation capabilities of the model, which is not desirable and error prone because they are outside of the validated space.

Statistics such as the Hotelling's T^2 and the Q residuals (Q_r) can be used to track sample variability as the first will test the membership of an observation to the population forming the calibration set and the second will determine the modeling error (or unmodeled features).[3] Samples presenting large values in these statistics can be subsequently evaluated to determine the source of the anomalously large T^2 or Q_r value.

It is necessary to investigate why the samples were different from the population used in calibration. Reasons can range from sample presentation or gross hardware issues to environmental effects, instrument aging, or sample modifications. To compensate for these issues, it is often necessary to perform calibration maintenance by adding the new encountered variability to the calibration set, adapting the preprocessing methods, optimizing the regression model, correcting predictions *a posteriori*, and so on.[4,5]

In many manufacturing settings, calibration updates are current, accepted, and justified by product characteristics. However, highly regulated fields such as the pharmaceutical industry are limited in their actions. The current pharmaceutical industry standards accept with difficulty the modification of an approved method.[6] The submission of a modification to regulators can be a lengthy procedure and can give the impression that the production process was not well understood and controlled by the sponsor prior to the original submission. Thus, there is a real need for chemometricians to carefully assess the risks associated with future samples' variability and find approaches to mitigate the effects on the predicted values.

The reasons for which two pharmaceutical batches will not be similar are often categorized into two groups: variability in the raw materials and process variability. No two lots of excipient will have the same exact properties.[7] The variability in raw materials used to produce excipients will inevitably cause differences in the final product. Although these differences might still be included in the design space and might not impact critical quality attributes enough to cause a batch failure, they will have consequences on drug manufacturing. Also, even if the active ingredients(s) and excipients were identical from batch to batch, no two granulations would be exactly alike, and no two blends would reach homogeneity at precisely the same time. Current pharmaceutical practices study these problems and

Correspondence to: Carl A. Anderson (Telephone: +412-396-1102; Fax: +412-396-1608; E-mail: andersonca@duq.edu)

Journal of Pharmaceutical Sciences, Vol. 103, 545–556 (2014)

more and more submissions to regulators include Quality by Design approaches where all relevant sources of variability are documented and characterized with respect to their impact on the drug product quality and efficacy.[8] However, it is not reasonable to accept that all sources of variability that can impact a process have been considered during the initial submission.

From the stand point of a NIR calibration model, the same problems must be considered. Instrumental effects (instrument drift and aging, lamp changes, etc.), environmental effects (changes in relative humidity in storage facilities), and active ingredient(s) and excipients variability are very likely to affect long-term prediction abilities. In the present study, the effects of instrumental aging, excipient particle size distribution, excipient manufacturer variability, and active ingredient physical transformation were studied. The evaluation of these effects is expressed in terms of the evolution of prediction precision and accuracy. The detection ability of these formulation changes will be assessed using Hotelling's T^2 and Q residual as diagnostic tools.

MATERIAL AND METHODS

Samples

Calibration Set

A fully balanced, quaternary mixture design comprising theophylline anhydrous (lot no. 92577; Knoll AG, Ludwigshafen, Germany), lactose 316 Fast Flo NF Monohydrate (lot no. 8502113061; Hansen Labs, New Berlin, Wisconsin), microcrystalline cellulose (MCC; Avicel PH-200; lot no. M427C; FMC BioPolymer, Mechanicsburgh, Pennsylvania), and soluble starch GR (lot no. 39362; EMD Chemicals Inc., Gibbstown, New Jersey) was generated. The approximate median particle size of the theophylline, lactose, MCC, and starch (reported by documentation from their respective suppliers) was 90, 100, 180, and 17 μm, respectively. Twenty-nine design points were chosen to cover a wide range in all constituents and to minimize the potential for factor aliasing.

The materials were mixed in 25 mL glass scintillation vials for 10 min by placing them on the rotating drive assembly of a Jar Mill (US Stoneware, East Palestine, Ohio). The blending time was chosen in accordance with a previous study that used a NIR-based prediction approach to estimate the homogeneity of similar blends.[9] The mixtures from each design point were then subdivided and compacted at two of five pressures (67.0, 117.3, 167.6, 217.8, and 268.1 MPa), randomly selected, on a Carver Automatic Tablet Press (Model 3887.1SD0A00; Wabash, Indiana) using a 13-mm die and flat-faced punches. The same mixture was used to create the tablets for each design point. The dwell time was set to 10 s. In total, 58 compacts were produced with a nominal target weight of 800 mg per compact. Table 1 summarizes the design.

Test Set

Two sets of 12 test runs each (with three repeats each; total of 72 compacts) were created with varying raw material properties. Samples were prepared over a period of 12 weeks (one run per week). The two sets corresponded to the two

Table 1. Quaternary Mixture Design Used to Produce Calibration Compacts (w/w)

Design Points	Anhydrous Theophylline	Lactose Monohydrate	MCC	Soluble Starch	Compression Force (MPa)[a]
1	0.600	0.200	0.200	0.000	117.3/217.8
2	0.400	0.400	0.201	0.000	67.0/268.1
3	0.201	0.599	0.200	0.000	268.1/268.1
4	0.400	0.201	0.399	0.000	217.8/217.8
5	0.200	0.400	0.399	0.000	67.0/117.3
6	0.200	0.200	0.600	0.000	67.0/167.6
7	0.600	0.200	0.000	0.199	67.0217.8
8	0.398	0.401	0.000	0.201	67.0/167.6
9	0.201	0.599	0.000	0.200	117.3/217.8
10	0.600	0.000	0.199	0.200	67.0/67.0
11	0.400	0.201	0.200	0.199	167.6/268.1
12	0.200	0.400	0.200	0.199	67.0/117.3
13	0.000	0.599	0.200	0.200	67.0/268.1
14	0.399	0.000	0.401	0.200	217.8/268.1
15	0.200	0.200	0.400	0.200	117.3/268.1
16	0.000	0.400	0.399	0.200	117.3/117.3
17	0.201	0.000	0.599	0.201	117.3/217.8
18	0.000	0.200	0.599	0.200	67.0/167.6
19	0.400	0.200	0.000	0.400	67.0/268.1
20	0.201	0.400	0.000	0.400	67.0/167.6
21	0.400	0.000	0.200	0.400	268.1/268.1
22	0.201	0.200	0.200	0.399	167.6/217.8
23	0.000	0.400	0.200	0.400	117.3/268.1
24	0.201	0.000	0.399	0.400	67.0/217.8
25	0.000	0.200	0.400	0.400	117.3/117.3
26	0.199	0.200	0.000	0.600	167.6/217.8
27	0.201	0.000	0.199	0.600	117.3/217.8
28	0.000	0.200	0.200	0.600	67.0/268.1
29	0.250	0.250	0.250	0.249	167.3/217.8

[a]Two compact produced by design point, selected at random.

 DOI 10.1002/jps.23816