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Lubricant-Sensitivity Assessment of SPRESS® B820 by Near-Infrared Spectroscopy: A Comparison of Multivariate Methods

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ABSTRACT

The predictability of multivariate calibration models, calculated with *offline* near-infrared spectroscopy (NIRS), assessing impact of magnesium stearate (MgSt) fraction, blending time, and compression force on the tablet breaking force (TBF) of SPRESS® B820 was statistically compared. Tablets of lubricated SPRESS® B820 were prepared by varying lubrication and compression conditions using 2^4 full factorial design. Tablets were scanned in reflection mode on a benchtop NIRS. A qualitative principal component analysis and quantitative principal component regression (PCR) and partial least square (PLS) regression relationship between lubricant concentration, blending time, compression force, preprocessed NIR spectra, and measured TBF was calculated with calibration data set. The predictability of calibration models was validated with independent data set. Expected qualitative correlations between MgSt blending time and TBF and a nonlinear relationship between MgSt fraction and TBF were observed. Predictability of PLS comprehensive (0.25%-1% w/w MgSt) model was significantly different from individual 0.25%, 0.5%, and 1.0% w/w MgSt PLS models. In addition, PLS calibration models' predictability was different from PCR calibration models. Thus, added lubrication fraction and adopted multivariate methodology should be selected carefully during the calibration and validation stages as it may have a significant impact on the predictability of the developed models.

Introduction

Near-infrared spectroscopy (NIRS) is a well-established analytical tool to monitor pharmaceutical processes *offline*, *atline*, or *inline*. Its popularity is in part because of its speed, convenience, minimal sample preparation, and noninvasive nature.[1] NIRS has also found applications in the analysis of physical and chemical properties of pharmaceutical raw materials and finished dosage forms. This wide spectrum of applicability makes NIRS an integral part of the pharmaceutical product development for assessing and monitoring the pharmaceutical product quality, specifically after inception of the Process Analytical Technology and International Conference of Harmonization Q8 Quality by Design guidelines.[2]

Although NIRS offers several advantages for pharmaceutical process monitoring, this technique generates enormous amount of data set. The large data generated require an appropriate and efficient management using statistical methods. This is a critical step for the success and applicability of NIRS. The developed models are expected to show sufficient robustness during implementation for the process monitoring. This can be feasible with the inclusion of all possible variations in the physical and chemical attributes of the analyzed sample during the model development. As a consequence, NIRS along with chemometrics-assisted model development has resulted in widespread pharmaceutical applications in research, production, product quality assessment, and control.[3] In addition, various critical pharmaceutical unit operations associated with solid dosage forms, such as powder blending, drying, wet granulation, and film coating, have been monitored successfully by NIRS.[4-11]

Magnesium stearate (MgSt) is among the most popular lubricants used in solid oral dosage forms, particularly tablet manufacture to reduce several tableting issues, such as picking, sticking, capping, lamination, and others.[12] However, prediction of MgSt lubrication efficiency is a complex process as it is a function of MgSt intrinsic properties, adopted lubrication conditions like MgSt fraction and blending time, as well as the intrinsic properties of host particles.[13]

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NIRS has been used to assess and monitor the complex lubrication performance of MgSt.[14-17] These mentioned studies have limitations due to their unidimensional nature and utilization of a single lubrication parameter or a univariate mathematical method. Most studies have also used either principal component regression (PCR) or partial least square (PLS) regression methods for data management, using the same data set for calibration and validation of model. This can result in a false predictive performance or overaccuracy of the model during validation stage. Such models might have poor predictability when tested on an independent data set in a real-life scenario.

The complex phenomenon associated with MgSt lubrication requires simultaneous analysis of the effect of lubricant parameters and tableting parameters together on the tablet properties. Thus, a synchronous study of the impact of various lubrication parameters on the MgSt lubrication efficacy with NIR monitoring might provide valuable insights for this unit operation. In addition, application of a univariate statistical treatment of the NIR data might not provide optimal results for the data management. Thus, a comparative evaluation of various multivariate methods to manage the data set generated during this study can help to develop an optimal robust modeling strategy.

The aim of the present investigation was to compare the predictive performance of PCR- and PLS-based calibration models developed with the data generated from NIRS used to monitor the impact of MgSt fraction, blending time, and compression force on the tablet breaking force of model material SPRESS® B820. The experimental conditions and MgSt-specific NIR spectra were used to develop qualitative and quantitative relationship with tablet breaking force using multivariate methods like principal component analysis (PCA), PCR, and PLS. The predictive performance of the developed PCR- and PLS-based calibration model was tested with a separate independent validation data set, which was not the part of calibration models.

Materials

Pregelatinized Corn Starch national formulary (SPRESS® B820; lot no. 51416376) was obtained from Grain Processing Corporation (Muscatine, IA). MgSt and national formulary (Hyqual®; vegetable source, lot no. 0000078281) were obtained from Avantor Performance Materials Inc. (Center Valley, PA).

Methods

Lubrication and Compression of Lubricated SPRESS® B820 Powder

Calibration Data Set

The MgSt fraction, blending time, and compression force were chosen as design variables, whereas tablet breaking force was used as a response variable (Table 1). A 2^4 full factorial experimental design with 1 constant variable (MgSt lubricant fraction) was used to assess the impact of MgSt on lubrication of SPRESS® B820. The MgSt blending time and compression force were varied for the same MgSt fraction. Additional higher blending time experiments were added to increase the experimental variation range. The laboratory-scale lubricated samples (~500 g) of SPRESS® B820 were prepared by an addition of MgSt. A preweighed quantity of starch powder was placed in a twin-shell blender (V-blender, 2-quart; Patterson-Kelley, East Stroudsburg, PA). The weighed quantity of MgSt was added directly to the blender via sifting through a #20 mesh (850-μm aperture) sieve. The mixture was blended for the selected blending time. The lubricated powder samples were compressed into tablets of 500 mg, target weight, on a 10-station instrumented rotary tablet press (Piccola™; SMI Inc., Lebanon, NJ), equipped with biconcave and unscored 10-mm B-tooling. SPRESS® B820 powders containing 0.25% w/w, and 1.00% w/w of MgSt, were blended for 2, 5, and 10 minutes. These tablets were compressed at 15, 20, and 25 kN compression force. SPRESS® B820 powders containing 0.50% w/w of MgSt were blended for 2, 5, and 10 minutes. The 2- and 5-minute blends were compressed at 15, 20, and 25 kN compression forces. The 10-minute blends of this sample were compressed at 25 kN compression force. Fifteen tablets were prepared for each set of lubrication and compression conditions.

Table 1
Experimental Conditions Implemented for the Development of Calibration Models

Batch Number	MgSt Content (% w/w)	Blending Time (min)	Compression Force (kN)	Tablet Breaking Force (kN)
1	0.25	2	15	119.58 (5.40)[a]
2	0.25	2	20	127.29 (7.15)
3	0.25	2	25	122.67 (12.71)
4	0.25	5	15	88.65 (5.28)
5	0.25	5	20	94.80 (3.39)
6	0.25	5	25	102.25 (2.68)
7	0.25	10	15	53.02 (4.36)
8	0.25	10	20	61.95 (2.20)
9	0.25	10	25	64.99 (3.30)
10	0.50	2	15	75.97 (3.19)
11	0.50	2	20	79.04 (3.70)
12	0.50	2	25	82.25 (2.64)
13	0.50	5	15	42.95 (3.24)
14	0.50	5	20	45.83 (2.81)
15	0.50	5	25	45.57 (2.64)
16	0.50	10	25	24.45 (2.63)
17	1.00	2	15	126.83 (5.13)
18	1.00	2	20	146.58 (9.32)
19	1.00	2	25	134.35 (5.11)
20	1.00	5	15	86.76 (4.72)
21	1.00	5	20	81.72 (5.25)
22	1.00	5	25	104.02 (4.99)
23	1.00	10	15	61.72 (4.80)
24	1.00	10	20	74.14 (4.06)
25	1.00	10	25	78.45 (3.27)

[a] Numbers in parentheses indicate SD ($n = 15$).

Independent Verification Data Set

Separate lubrication and compression conditions were chosen to develop validation data set (Table 2). SPRESS® B820 powders lubricated with 0.25% w/w MgSt were blended for 1 minute. This powder was compressed at 10, 15, 20, and 25 kN compression force.

Table 2
Experimental Conditions Implemented for the Validation of the Developed Models

Batch Number	MgSt Content (% w/w)	Blending Time (min)	Compression Force (kN)	Tablet Breaking Force (kN)
1	0.25	1	10	82.38 (5.41)[a]
2	0.25	1	15	101.86 (4.14)
3	0.25	1	20	134.29 (4.65)
4	0.25	1	25	145.53 (5.57)
5	0.25	2	10	73.62 (3.70)
6	0.25	5	10	64.59 (4.66)
7	0.25	10	10	39.03 (2.32)
8	0.50	1	10	68.71 (3.86)
9	0.50	1	15	95.32 (3.93)
10	0.50	1	20	118.01 (4.29)
11	0.50	1	25	106.76 (4.66)
12	0.50	2	10	59.82 (7.72)
13	1.00	1	10	46.61 (2.62)
14	1.00	1	15	72.18 (6.63)
15	1.00	1	20	77.01 (4.46)
16	1.00	1	25	57.01 (7.18)
17	1.00	5	10	43.80 (2.69)
18	1.00	10	10	30.47 (2.05)

[a] Numbers in parentheses indicate SD ($n = 15$).