A novel application of near infrared universal quantitative models in pharmaceutical process analytical technology (PAT)

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Introduction

Constructing a successful near infrared (NIR) spectroscopic model for pharmaceutical process analytical technology (PAT) is a complex, resource-consuming task that is restricted by sample collection and model optimisation. The costs and limitations of developing models can be prohibitive, and few pharmaceutical manufacturers[1] have accepted NIR as a PAT tool in China. In contrast, universal quantitative NIR models established by the National Institutes for Food and Drug Control (NIFDC) have been widely used for screening counterfeit drugs in the Chinese market since 2006. The calibration set for these universal models included different samples with the same international non-proprietary name (INN) produced by different manufacturers. Differences within the calibration set can arise from changes in both the physical properties (particle size, grain size distribution, compactness etc.) and active pharmaceutical ingredient (API) concentrations. Hence, there is a wider sample range in the universal model than in the general model. If the universal model was used for PAT, then difficulties in collecting appropriate sample sets for constructing initial calibration models could be resolved. In this study, the universal NIR quantitative model for erythromycin ethylsuccinate tablets was corrected and used to quantify powder mixtures before tabletting in Xi'an Lijun Pharmaceutical Co., Ltd. China. Our results show that the accuracy of the universal quantitative model is comparable to the official legal method.

Materials and Methods

Apparatus and software

Data were collected with a MATRIX-F FT-NIR spectrometer (Bruker Optik GmbH, Ettlingen, Germany), equipped with a 1.5 m fibre-optic diffuse reflectance probe and an extended thermoelectrically-cooled indium gallium arsenide (InGaAs) detector. Spectral collection and chemometric processing were performed with OPUS 6.5 (Bruker Optik GmbH, Ettlingen, Germany).

Samples

Measurements were made on Lijunsha® (erythromycin ethylsuccinate tablets; Xi'an Lijun Pharmaceutical Co., Ltd., China). Batches (n = 10) of powder mixtures measured before and after tabletting were used to establish a piecewise direct standardisation correction (PDS) spectra transfer method and a slope/bias (S/B) correction function. The powder mixtures had the same components as their corresponding tablets. 17 subsequent batches were used as validation set and another 10 batches were analysed on site in the Xi'an Lijun Pharmaceutical company factory. The reference API contents of erythromycin ethylsuccinate were analysed by biological assay.[2]

NIR spectroscopy

Diffuse reflectance spectra were recorded at 8 cm^{-1} resolution with 32 co-added scans over the spectral range of 4000–12000 cm^{-1}. Three NIR spectra were recorded per sample and the average spectrum was used for the model construction or analysis.

NIR universal model for erythromycin ethylsuccinate tablets

The universal quantitative model[3] for erythromycin ethylsuccinate tablets was constructed by NIFDC. 198 batches of erythromycin ethylsuccinate tablets from 36 different Chinese manufacturers were used for model construction; 6 batches of Lijunsha® were included in the calibration and validation set (Table 1).

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Table 1. Parameters of the universal quantitative model for erythromycin ethylsuccinate tablets.

	Calibration	Validation
Samples	132	66
Concentration range (%)	25.47–70.86	43.32–65.67
Wavelength range (cm^{-1})	6248.4–5446.2	
Spectra pre-treatment	1st derivative, vector normalisation	
Rank	6	
R^2 (%)	95.38	85.89
RMSECV(P)	2.29	2.13

Results and Discussion

PDS spectra transfer method

The PDS[3] algorithm standardises differences in absorption intensity, wavenumber shift and peak broadening between spectra obtained on different spectrometers. PDS has proven useful for transferring calibrations between different spectrometers,[5-8] at different temperatures,[9] and with different powder injection methods.[10] Here, the PDS algorithm was applied to transfer calibration models between the final powder mixtures before tabletting and their corresponding tablets. Spectra from tablets were used as 'master' spectra, whereas powder mixtures were 'slave' spectra. Window size was set at 7.

Powder batches (n = 17) were used as external validation samples. The Mahalanobis distance[11] is usually used to detect outliers and can be calculated in the relevant subspace spanned by the calibration PLS vectors. The threshold of Mahalanobis distance of the universal model was set at 0.14 to identify the outliers. This distance was decreased greatly and all the identifications were correct after PDS (Table 2). However, there was no significant change in the NIR predictions before and after PDS, indicating the need for a subsequent correction method.

Table 2. Results before and after PDS.

No.	Reference (%)	NIR prediction (%)		Mahalanobis distance	
		Before PDS	After PDS	Before PDS	After PDS
1	60.98	62.85	63.20	0.17	0.083
2	60.69	62.50	62.99	0.23	0.1
3	61.07	62.17	62.92	0.21	0.093
4	61.60	62.86	63.25	0.21	0.1
5	60.36	63.35	63.51	0.23	0.11
6	61.18	63.04	63.40	0.19	0.088
7	61.92	62.90	63.27	0.21	0.1
8	59.85	62.21	62.68	0.16	0.088
9	60.75	61.82	62.62	0.24	0.1
10	60.34	63.24	63.13	0.092	0.087
11	60.02	62.55	62.81	0.071	0.065
12	61.79	63.59	63.51	0.085	0.068
13	60.39	62.07	62.62	0.14	0.085
14	63.65	63.13	63.31	0.13	0.082
15	61.95	62.83	63.09	0.13	0.08
16	61.52	62.49	62.94	0.17	0.1
17	60.73	61.56	62.35	0.13	0.067

S/B correction method

This is a simple univariate standardisation technique which establishes a linear regression between X and Y. X and Y are the concentrations predicted by the model with the responses of the reference samples in the first and the second experimental conditions, respectively[12]. Here the true values of the 10 reference batches of tablets and their direct predictions of the universal model were used as Y and X to construct a linear regression ($y = 1.1392x - 10.65$, $r = 71\%$). The PDS-corrected spectra were first quantified by the universal model and then corrected with the S/B regression function.

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External validation

Batches (n = 17) of the final powder mixtures of Lijunsha® were evaluated in order to validate the accuracy of the universal model after the two-step correction (Table 3). The maximum bias in the prediction between the two step corrected samples and the corresponding reference value was 2.17%, and the average absolute bias was 0.60%.

Biological assay is the official legal method for analysing the API content of erythromycin ethylsuccinate. Biological assays are time-consuming and the techniques and interpretations can vary with different operators in spite of the rigid requirements specified by official publications. The permissible error for this method can reach to 5% (personal observations). Our results show that the universal quantitative model can produce accuracy comparable to that of the biological assay.

Table 3. External validation results.

No.	API Content (%)				
	True	NIR Prediction			
		Original spectra	Bias from reference	Spectra after PDS and SB	Bias from reference
1	60.98	62.85	1.87	61.35	0.37
2	60.69	62.50	1.81	61.11	0.42
3	61.07	62.17	1.10	61.02	-0.05
4	61.60	62.86	1.26	61.40	-0.20
5	60.36	63.35	2.99	61.70	1.34
6	61.18	63.04	1.86	61.58	0.40
7	61.92	62.90	0.98	61.42	-0.50
8	59.85	62.21	2.36	60.76	0.91
9	60.75	61.82	1.07	60.68	-0.07
10	60.34	63.24	2.90	61.26	0.92
11	60.02	62.55	2.53	60.91	0.89
12	61.79	63.59	1.80	61.70	-0.09
13	60.39	62.07	1.68	60.69	0.30
14	63.65	63.13	-0.52	61.48	-2.17
15	61.95	62.83	0.88	61.22	-0.73
16	61.52	62.49	0.97	61.05	-0.47
17	60.73	61.56	0.83	60.38	-0.35

Table 4. The results for actual application.

Batch No.	API Content (%)		
	Official method	NIR method	Bias
1012602-1	60.70	61.48	0.78
1012602-2	60.76	61.00	0.24
1012002-4	60.33	60.93	0.60
1012002-5	59.90	61.69	1.79
1012002-7	60.20	61.16	0.96
1012002-8	60.14	62.17	2.03
1101001-4	60.57	61.85	1.28
1101001-6	60.08	61.02	0.94
1101001-8	60.82	61.91	1.09
1101097-2	59.53	62.34	2.81

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Actual application

To simplify all the correction steps, a programme was compiled using the MACRO function in OPUS 6.5, which can automatically perform all commands from recording spectra to giving the final correction result. An instrument (MATRIX-F) equipped with this program was used to analyse Lijunsha® powder mixtures (before tabletting) in the Xi'an Lijun Pharmaceutical company factory. Table 4 shows the NIR prediction results for the first 10 batches and all results show that the corrected universal model can reach the same accuracy as the biological assay.

Conclusion

This study provided a novel application of NIR universal quantitative models in pharmaceutical PAT. The application of such models during the construction of initial PAT frameworks could save pharmaceutical manufacturers time and other resources.

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