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Near infrared spectroscopy and process analytical technology to master the process of busulfan paediatric capsules in a university hospital

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Abstract

The prescription of unlicensed oral medicines in paediatrics leads the hospital pharmacists to compound hard capsules, such as busulfan, an alkylating agent prescribed in preparative regimens for bone marrow transplantation. In this study, we have investigated how the general principle of process analytical technology (PAT) can be implemented at the small size of our hospital pharmacy manufacturing unit.

Near infrared spectroscopy (NIRS) was calibrated for raw material identification, blend uniformity analysis and final content uniformity of busulfan hard capsules of 11 different strengths. Measurements were performed on capsules from 2 to 40 mg ($n = 440$). After optimisation, accuracy and linearity of the NIRS quantitative method was demonstrated after comparison with a previously validated quantitative high performance thin layer chromatography (HPTLC) method. Such a comparison led to attractive NIRS precision: ±0.7 to ±1.0 mg for capsules from 2 to 40 mg, respectively.

As NIRS is a rapid and non-destructive technique, the individual control of a whole batch of busulfan paediatric capsules intended to be administrated is possible. Actually, mastering the process of busulfan paediatric capsules with the NIRS integrated into the notion of PAT is a powerful analytical tool to assess the process quality and to perform content uniformity of at least 5 mg busulfan-containing capsules.

Keywords: NIRS; Paediatrics; Busulfan; PAT; Manufacturing

1. Introduction

The prescription of unlicensed or off label medicines has been widely reported in paediatric practice [1–5] and is likely to be hazardous to children. Indeed, the hospital pharmacy often compounds oral magistral or extemporaneous preparations [6,7], such as busulfan-containing capsules, an alkylating agent prescribed in preparative regimens for bone marrow transplantation in patients with haematological malignancies, solid tumors and non-malignant disorders. Busulfan (1,4-butanediol dimethanesulfonate) is administered orally in doses of 1 mg kg^{-1}, every 6 h for 4 days. This chemotherapeutic agent belongs to the series of the alkanesulfonic acid esters ($CH_3SO_2O(CH_2)_4OSO_2CH_3$) possessing significant cytotoxic activity essentially expressed by haematological toxicity. The major toxic effect of busulfan, reported when administered with high doses of cyclophosphamide, includes hepatic veno-occlusive disease with a mean incidence of 20–30% [8].

Considering the narrow therapeutic index of this drug and its variable bioavailability related to variable absorption and clearance in young children, pharmacokinetic monitoring is recommended. Using population pharmacokinetic models and Bayesian fitting algorithms, Bleyzac et al. managed to decrease the busulfan doses prescribed for 67% of their patients, and to reduce significantly the incidence of veno-occlusive disease by performing a daily evaluation of busulfan plasma concentrations

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[8]. In this context, the manufacturing process of such potent drug preparations must be carefully quality assured to ensure the accuracy and relevance of pharmacokinetic studies.

It is acknowledged that busulfan is difficult to quantify because of its poor ultra violet (UV) or visible absorption and its instability in aqueous solution. Several methods have been developed for the quantification of busulfan, such as gas chromatography with electron capture detection (GC–ECD) [9,10], high performance liquid chromatography (HPLC) coupled to derivatisation with UV detection [11–13], gas chromatography coupled to mass spectrometry (GC–MS) after derivatisation [14–16], HPLC coupled to mass spectrometry (HPLC–MS) without derivatisation [17,18] and eventually, high performance thin layer chromatography (HPTLC) with a derivatisation procedure [19]. All these methods are difficult to set up, time-consuming, require reagents or consumable parts and are all sample destructive. Thus, they can only be used as a final control.

Near infrared spectroscopy (NIRS) is considered as a quantitative and non-destructive method used for routine identification and quality testing of incoming raw materials [20–22], and content determination of active compounds in pharmaceutical preparations [23,24]. In this context, NIRS is described as a process analytical tool, perfectly integrated into the notion of process analytical technology (PAT) [25,26], a new concept oriented towards industrial production for designing, analysing, and controlling manufacturing through timely measurement of critical quality steps with the goal of ensuring final product quality [27]. NIRS has already proved its efficiency in the understanding of a manufacturing problem [28,29], in improving the control laboratory quality [30,31], and allowing non-destructive dissolution analysis during formulation [32], or hardness testing of solid formulations [33]. The aim of this study was to validate the NIRS method in controlling the manufacturing process, at the small size of hospital pharmacy batches, as well as ensuring the content uniformity of busulfan hard capsules made at Robert Debré children's hospital.

2. Materials and methods

2.1. Capsule manufacturing process and content uniformity by HPTLC [19]

Capsules no. 5; 0.13 mL (LGA, La Seyne, France) were prepared according to good manufacturing practice, from two different batches of busulfan powder (Farhaus Pharma GmbH, Hambourg, Germany) diluted with lactose (AGEPS, Paris, France). Seventeen batches of 50 capsules were made with semi-automatic capsules fillers (LGA) at 11 different strengths—2, 3.5, 5, 7.5, 10, 15, 20, 25, 30, 35 and 40 mg. Each capsule was weighed and identified for subsequent steps of analysis. Additionally, those batches complied with mass uniformity tests (Vth European Pharmacopeia, 2.9.40). Twenty to forty capsules from each batch were tested on content uniformity according to HPTLC method [19], previously validated in terms of accuracy ($\leq$4%), precision (relative standard deviations, R.S.D. $\leq$ 5%), linearity ($R^2 > 0.99$), selectivity and specificity.

2.2. NIRS

NIRS relies on the absorption of near infrared radiation (800–2500 nm) by the organic material. NIR absorption is due to vibrational overtone and combination bands which are correlated to fundamental C–H, N–H, O–H and S–H vibrations originating in the mid infrared region. These vibrations are complex functions of physical and chemical parameters that have to be resolved by chemometric methods [34,35]. Because multivariate calibrations generate non-redundant orthogonal latent variables, the advantages stand on noise reduction, outlier control and mathematical selectivity. The vast amount of information collected in a spectrum is hence reduced into a simplified data set containing the most relevant information after change of variables.

2.3. Raw material identification and blend uniformity analysis using NIRS

An identification of busulfan and lactose samples was first carried out by comparing the mid infrared spectra to literature data. Spectra of pure busulfan and pure lactose were recorded and introduced in a NIRS library containing other active components and excipients. The NIRS qualitative analysis was carried out by performing a cluster analysis. The three key elements characterising the raw material identification are as follows:

- spectra from a particular raw material should appear as a unique cluster;
- the size of clusters should be consistent and as small as possible;
- clusters should be as far as possible from each other.

The blend was obtained by mixing busulfan and lactose powders in a mortar by manual rotation of the pestle. At different steps of the mixing, spectra ($n = 42$) were recorded in the wave number range of 4000–10,000 cm^{-1} (data interval, 12 cm^{-1}) with three scans at different selected spots at random in the mortar with a BÜCHI NIRFlex N-400 FT-NIR® spectrometer (Flawil, Switzerland). Results were expressed by area differences between each spectrum and the homogeneous blend spectrum versus the number of manual rotations, using full wave number range. This spectrometer is equipped with a reflectance fibre optical probe module, a 10 W light source and a PbS detector maintained at 30 °C.

2.4. Procedure for the determination of content uniformity in capsules by NIRS

Transmittance spectra of all capsules ($n = 440$) were recorded with a BÜCHI NIRTab® system using a flexible sample plate with 3 mm aperture (3 mm Spectralon reference), 10 mm optical tube, a 90 W light source, a 1 m optic fiber as connection between autosampler and spectrometer module and an indium gallium arsenide (InGaAs) detector cooled at 0 °C.

All capsules were measured by placing them onto the 40 positions sample wheel alternately top part pointing outwards

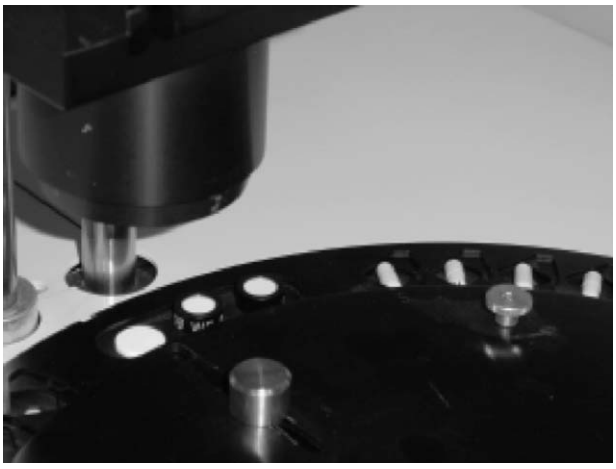

Fig. 1. Experimental setting for capsule measurement with transmittance acquisitions.

(Fig. 1), in the wave number range of 6000–11,520 cm^{-1} (data interval, 12 cm^{-1}).

Five scans were measured for 240 capsules (busulfan-containing capsules of 2, 5, 10, 20, 30 and 40 mg) while 10 scans were recorded for the other 200 capsules (i.e. busulfan-containing capsules of 3.5, 7.5, 15, 25 and 35 mg) in order to compare those two acquisition methods. Data acquisition was performed with BÜCHI NIRCal® 3.04 Chemometric Software. Calculation and optimisation were performed with BÜCHI NIRCal® 4.21 Chemometric Software and Unscrambler® 6.11 b (Camo Process AS, Oslo, Norway).

The model validation and optimisation were performed according to the Vth European Pharmacopoeia (2.2.40) [36] and to the guidelines on analytical validation [37,38] and implementation of NIRS [39].

A partial least squares (PLS) regression was used to calculate the busulfan content of capsules from their NIR spectra. Two-third of the spectra of each strength were assigned to the calibration set used to establish the PLS model. The remaining spectra were included in a validation set used to evaluate the ability of the PLS model to predict the busulfan content of capsules from their NIR spectra.

According to the calculation principles used in the Nircal software, the PLS factors are used in two distinct ways:

- A first number of factors are chosen, with respect to, the predicted residual sum squared of all spectra over all factors (XPRESS). At this stage, the purpose is spectra modelling. These factors called "primary factors" allow definition of an acceptable spectra residual. When using the PLS model to predict the busulfan content of capsules from their spectra, the spectra residual is used to evaluate the similarity between these spectra and the calibration set. This feature is similar to an identity check of the sample prior to its quantification.
- A lower number of "secondary factors" are chosen among the primary factors in order to establish the relationship between spectra and busulfan content. The result is expressed as the prediction ability of NIRS, with respect to, the (reference) method used to assay the busulfan content in capsules from both the calibration and the validation sets. First, the correlation coefficient between the NIRS prediction and the reference method is to be maximised. Then, the standard error of estimate (SEE, calibration set) and standard error of prediction values (SEP, validation set) are to be lowered down to ≈1.4 times the standard error of the reference method [39]. The SEE to SEP ratio (called "consistency" in the Nircal software) close to unity is also used as a criterion to ensure that no overfitting of the calibration set occurred.

The NIRS precision was assessed by SEP (mg) values and R.S.D. (%) of repeatability and reproducibility studies. Meanwhile, measuring spectra with a stated number of scans (5 or 10), a repeatability study was performed in minimal conditions of variation, by measuring the same capsule six consecutive times. The reproducibility assay was performed in maximal conditions of variation in our laboratory, by measuring the same capsule on different positions of the carrousel at different times of the day.

Calibration and validation curves represent the predicted NIRS values versus the HPTLC reference values. Accuracy and linearity between the two quantitative methods were assessed with the determination of regression slopes and bias (average differences between the NIRS values and the values from the reference method for the same samples).

The robustness was assessed during 1-year period.

3. Results and discussion

3.1. Measurements in HPTLC

According to the Vth European Pharmacopoeia, when the active drug of a unit dose pharmaceutical form is less than 25 mg or 25%, a content uniformity assay has to be performed. Capsules fulfil the requirements if 10 units of one batch are quantified within the 85–115% range (European Pharmacopoeia, fifth ed.,

Table 1
HPTLC uniformity content of the 11 batches of busulfan-containing capsules ($n = 440$)

Theoretical strength (mg)	2.00	3.50	5.00	7.50	10.00	15.00	20.00	25.00	30.00	35.00	40.00
HPTLC average content (mg)	2.00	3.53	4.92	7.59	10.05	15.02	19.95	25.30	31.02	34.25	39.63
S.E.[a] (mg)	0.13	0.11	0.14	0.26	0.53	0.74	0.88	1.13	1.00	1.35	1.80
R.S.D.[b] (%)	6.5	3.1	2.9	3.4	5.3	4.9	4.4	4.5	3.2	3.9	4.6
Drug dilution[c] (%)	1.7	3.2	4.4	6.9	9.5	14.3	17.3	23.9	28.1	32.0	38.5

[a] S.E., standard error.
[b] R.S.D., relative standard deviation.
[c] Drug dilution, percentage of active component in capsule (w/w).

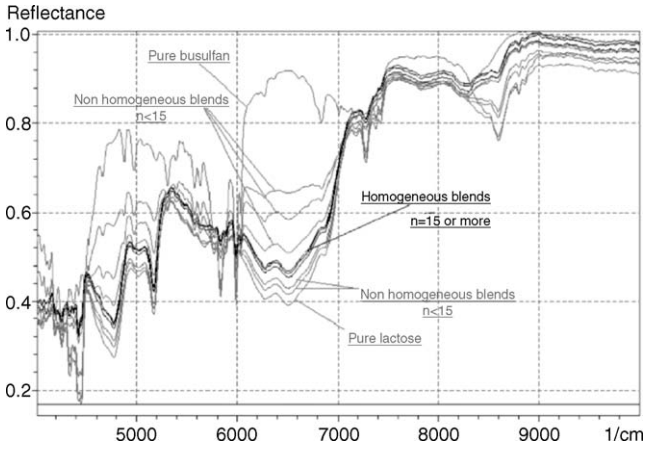

Fig. 2. Spectra recorded during blending of busulfan and lactose by manual rotations (n = number of manual rotations, 2–300).

2.9.40). Data obtained for the content measurement of 440 capsules by HPTLC are summarised in Table 1.

According to the content uniformity determined by HPTLC, all batches passed the European Pharmacopoeia test. S.E. for HPTLC content determination spread out from 0.11 to 1.80 mg (R.S.D. = 2.9–6.5%), which represents the variability of the manufacturing batches added to the HPTLC precision. As seen in Table 1, HPTLC precision is independent of the strength tested because each capsule was diluted in order to have the concentration set between 200 and 350 $\mu g\,mL^{-1}$.

3.2. Raw material identification and blend uniformity analysis

In the cluster analysis, the validation of the NIRS qualitative method was performed when minimal clusters radii and maximal distances between raw materials clusters (called Mahalanobis distances) were achieved. Indeed, no group overlapped in the map constituted by the three first principle components axes (data not shown).

The spectra of pure busulfan, pure lactose and several blends during the homogenisation by manual rotations (n = 2–300) were recorded and are presented in Fig. 2.

Area differences between each spectrum and the homogeneous blend spectrum were calculated, using full wave number range, at different steps of the mixing. These area differences decreased until the blend was homogeneous (after 15 manual rotations).

Formerly, carmin was used as a coloured tracer, although it is known that uniform coloured powder does not guarantee a homogeneous blend. Moreover, many colouring agents have been associated with hypersensitivity [40]. As NIRS can unambiguously be used as a homogeneity indicator, coloured tracer is not required anymore. This analytical technique, perfectly integrated in the PAT of blending, allows the standardisation of a small size hospital pharmacy manufacturing process. The blend homogeneity will no longer depend on the technician compounding the magistral or extemporaneous preparation.

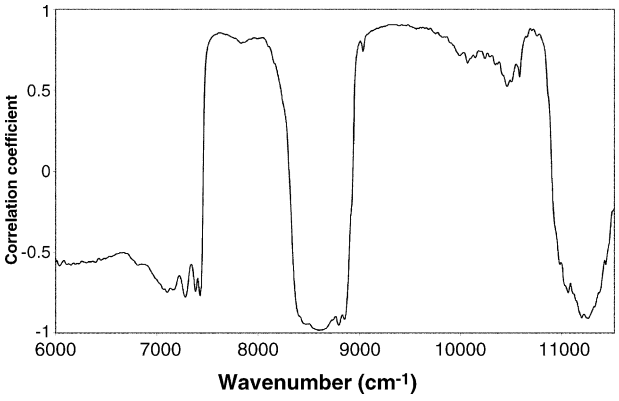

Fig. 3. Correlation plot between busulfan content and spectra pre-treated by normalisation to unit length and standard normal variate.

3.3. Quantification with transmittance acquisitions

Typical practice for NIR analysis states that the quantity of calibration samples used to validate a NIRS quantitative method must be between 20 and several 100s [41]. We chose to increase our sample number until precision and accuracy reached a plateau. Due to a weak signal to noise ratio (SNR) recorded for our samples, and the strength range to be covered, 440 samples were necessary to validate the content uniformity on a range from 5 to 35 mg busulfan-containing capsules, with a calibration range wider than the normal production range (2–40 mg) according to the European Medicines Agency guidelines [39].

The scans of hard capsules of busulfan, led to weak transmitted signals (transmittance values between 0.0 and 0.2 across spectra) with a poor SNR. Although an improvement of the SNR could have been possible by increasing the number of scans at the cost of measurement time, we preferred to favour the measurement time rather than the SNR.

Pre-processing methods help to minimise the large baseline shifts of NIR spectra, especially with powder samples which contain materials of various particle size distribution, different densities or different moisture content. The spectral pre-treatment was chosen, with respect to, the direct correlation between spectral response and busulfan content of capsules (Fig. 3). Combined pre-treatment with a normalisation to unit

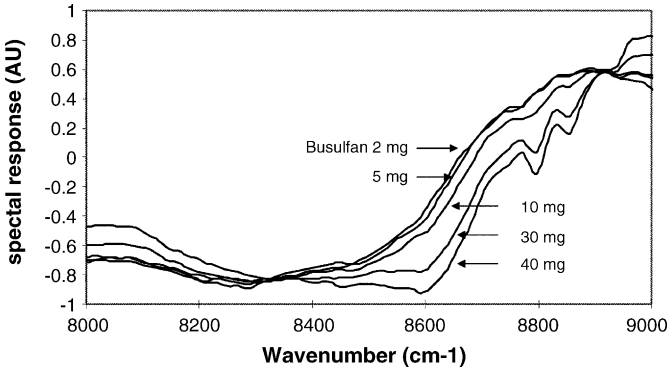

Fig. 4. Spectral changes based on the concentration of busulfan-containing capsules from 2 to 40 mg (pre-treated spectra, normalisation to unit length and standard normal variate).

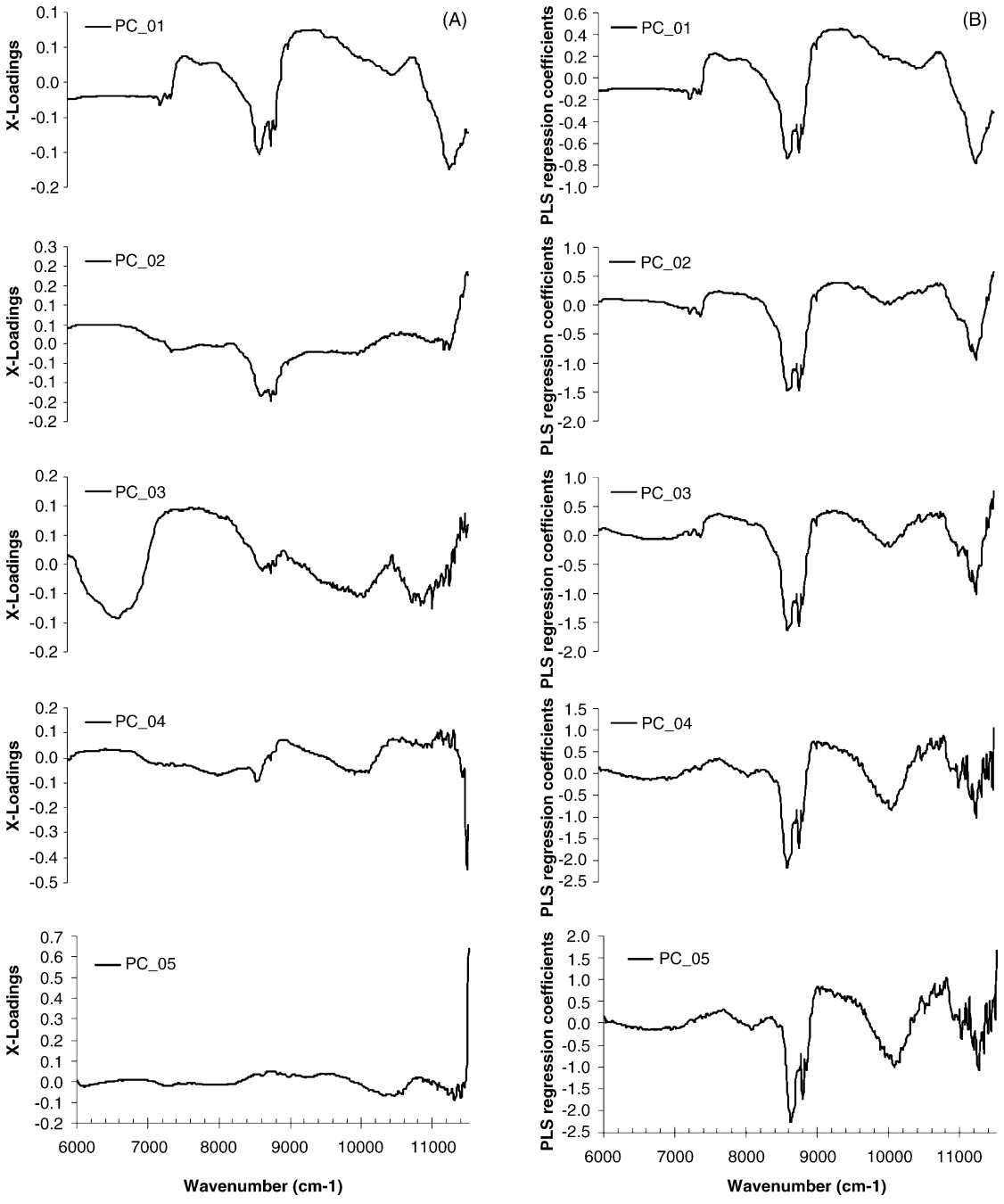

Fig. 5. Loadings (A) and PLS regression coefficients (B) against wave numbers for the five first principal components.

length followed by a standard normal variate was chosen. These pre-treatments are both known to correct the baseline shift in NIR spectra. However, their combination was found superior to the use of each of the pre-treatment alone. As seen from Fig. 3, some spectral areas show important correlation with busulfan content. After applying this pre-treatment, the spectral change based on the busulfan concentration could be observed along certain specific frequencies as illustrated on Fig. 4, representing spectral response (pre-treated spectra) versus wave numbers, obtained from 2 to 40 mg busulfan capsules for the strongly correlating region between 8000 and 9000 cm^{-1}. At these wavelengths, the relationship between busulfan content and spectral response is clearly demonstrated.

From its principle, the PLS regression allows computation of factors across the spectral range, chosen in a way to provide maximum correlation with quantitative properties associated with spectra. Wave number range narrowing improves the model performance.

As presented in Fig. 5(A), the loadings versus wave numbers show important variations indicating that the whole wave number range contain not only important variables with regard to spectral variation, but also noise above 11,000 cm^{-1}. The impor-

Table 2
Precision, accuracy and linearity results for transmittance assays obtained for capsules of 11 different strengths

PLS regressions summary				
	2–40 mg		2–15 mg	
	Calibration I	Validation I	Calibration II	Validation II
Number of spectra	277	131	148	74
Wavelength				
Acquisition	6000–11,520 cm^{-1}			
Calibration	6840–10,872 cm^{-1}			
Data pre-treatments	Normalisation to unit length standard normal variate			
Factors included in spectra modelling (primary factors)	14		14	
Factors included in PLS regression (secondary factors)	9		7	
SEE/SEP (mg)	1.04	1.07	0.44	0.66
Correlation coefficients	0.997	0.996	0.995	0.988
Regression slope	0.993 ± 0.005	0.990 ± 0.007	0.990 ± 0.009	0.982 ± 0.016
Regression *Y* intercept	0.12 ± 0.11	0.13 ± 0.15	0.08 ± 0.07	0.11 ± 0.14
Regression bias	0.00	0.04	0.00	0.02

tance of the correlation between spectral variation and busulfan content was then assessed by examining the PLS regression coefficients plotted against the wave numbers (Fig. 5(B)). Large absolute values of the coefficients indicate high correlation and show that the 6840–10,872 cm^{-1} region was favourable.

This last spectral range was then selected to calculate the PLS regression.

Nine factors were involved in the calibration established on the whole range (calibration I). As summarised in Table 2, the correlation coefficient expressing the relationship between the NIR method and the HPTLC reference method are close to 1, both for the calibration and validation sets. For both sets, the intercept is not significantly different from 0 and the slope is not different from 1 at the 5% risk. This results in a negligible bias for both sets.

Equal SEE and SEP values were found. As SEP is an indicator of the method precision, the value of 1.07 indicates that the NIRS method should be adequate to predict busulfan values in the 15 ∼ 20–40 mg range. For this range, a repeatability of about 5% can be expected.

In order to improve the calibration for lower busulfan content, a second calculation (calibration II) was done, by removing spectra in the 20–40 mg range from both calibration and validation sets. Seven factors were necessary to establish the calibration. The resulting correlation coefficients appeared to be lower (0.995 and 0.988 for the calibration and validation sets, respectively), than for the 2–40 mg range while the intercepts and slopes were again not significantly different from 0 and 1, respectively, at the 5% risk. The bias was also found negligible. The SEE and SEP were decreased to 0.44 and 0.66, respectively. Thus, this second calibration was used to predict busulfan content of capsules in the 2–10 mg range.

3.3.1. Accuracy and linearity

As part of the calibration development, the linearity of the NIRS method has already been validated. As shown in Table 2, the slopes of each calibration and validation curves were not significantly different from 1 at the 5% risk and the intercept did not differ either from 0 at the same risk level. In both full and reduced range calibrations, the bias appeared to be negligible. In Table 3, HPTLC contents and NIRS predicted contents were compared for a set of busulfan capsules not included in the previous calibrations (external calibration). As shown in Table 3, the results of the NIRS prediction appeared to be similar to the HPTLC results for both calibrations. A paired *t*-test was run on 25 samples with busulfan content, ranging from 2 to 10 mg, and predicted using calibration II. The mean of the differences between the NIRS and HPTLC values (0.03 mg) appeared not statistically different from 0 at the 5% risk. For the upper range of busulfan capsules, 30 samples were assayed using calibration I and the

Table 3
Comparison of reference HPTLC average with NIRS predicted busulfan contents (external validation)

Calibration	Range 2–10 mg ($n = 25$)		Range 15–40 mg ($n = 30$)	
Analytical method	HPTLC	NIRS	HPTLC	NIRS
Minimum (mg)	1.90	1.64	14.50	13.66
First quantile (mg)	3.60	3.98	20.13	20.30
Median (mg)	5.00	5.04	28.57	27.57
Mean (mg)	5.62	5.59	27.37	27.57
Third quantile (mg)	7.65	7.45	33.04	34.17
Maximum (mg)	10.20	10.44	40.50	40.17
Mean differences	0.03		−0.19	
Confidence interval (5% risk)	[−0.20; 0.26]		[−0.71; 0.32]	

Table 4
Results of repeatability and reproducibility assays performed on 11 strengths of busulfan-containing capsules using 5 and 10 scans

Capsule strengths (mg)	2[a]	3.5[a]	5[a]	7.5[a]	10[a]	15[b]	20[b]	25[b]	30[b]	35[b]	40[b]
Number of scans	5	10	5	10	5	10	5	10	5	10	5
R.S.D. (%) repeatability (max)	17.1	9.7	5.5	6.5	3.3	3.9	7.8	2.8	3.1	1.4	2.4
R.S.D. (%) reproducibility (max)	17.8	13.1	5.9	9.3	6.3	5.8	6.8	4.2	1.8	1.3	1.3

[a] 2–10 mg capsules predicted from calibration II.
[b] 15–40 mg capsules predicted from calibration I.

mean differences between NIRS and HPTLC (−0.19 mg) was not found different from 0 at the 5% statistical risk.

3.3.2. Precision

Results of repeatability and intermediate precisions for capsules, not included in either the calibration nor the validation set of the two previous calibrations, were assessed using NIRS. The results, presented in Table 4, were consistent with the precision expected from the SEE and SEP values of both calibrations.

For capsules in the 5–10 mg range, an adequate precision with a R.S.D. between 3.3 and 9.3% (in terms of repeatability or intermediate precision) could be achieved using calibration II. For the 15–40 mg capsules, the full range calibration allowed a precision of less than 5%, except for the 20 mg capsules. However, this last result is likely to be overestimated since the R.S.D. of repeatability (7.8%) was found higher than intermediate precision (6.8%).

According to the European Medicines Agency guideline on near infrared spectroscopy [39], the precision of the NIR method should be less or equal to 1.4 times the precision of the reference method. Thus, since the precision of HPTLC is approximately 5%, a precision of the NIRS of 7% could indeed be considered.

3.3.3. Robustness

Our data were collected over a 1-year period, which inserts a real life variability into our calibration. Borer et al. showed the influence of various factors such as the iris aperture, the number of data points, the orientation of the sample, the number of scans, the total number of samples, the reference frequency and the number of days over which the experiment is performed [42]. They confirm the importance of building libraries over a long period for maximum robustness by incorporating variation due to instrument drift.

4. Conclusion

Our optimised NIR calibration procedure is now suitable to obtain linear, accurate, precise and robust quantification models for busulfan-containing capsules from 5 to 35 mg with regard to low errors of prediction.

Indeed, if we calculate the NIRS repeatability S.E., from Table 4, for the 5 mg capsules, we find a 0.27 mg S.E. When comparing this NIRS S.E. to the reference ones for this 5 mg strength (R.S.D. = 5%, S.E. = 0.25 mg), our quantitative method passes the EMEA recommendation (as NIRS S.E. < 1.4 SEL) [39]. Moreover, when comparing S.E. repeatability results, calculated from Table 4, to SEP values (Table 2), one understands that our method may be more precise than estimated with the determination of SEP values (NIRS repeatability S.E. < SEP). Indeed, it must be kept in mind that the lack of precision of the reference method is always integrated into the NIRS calibration.

This range −5 to 35 mg busulfan-containing capsules exactly covers the prescriptions we have to face with in a paediatric hospital, due to the individual adaptation of posologies for each patient (1 mg kg^{-1}).

In such a context, with a narrow therapeutic index drug, the NIRS shows obvious advantages based on the rapidity of the analyses and their non-destructive character allowing the individual control of every single capsule, intended to be administered. Therefore, it contributes to the improvement of patient safety.

Our study also demonstrates the possible implementation of the process analytical technology concept at the scale of hospital production: from the identity and quality testing of incoming raw material, the blend uniformity analysis to the final content uniformity. Integrated in our manufacturing operation with the NIRS, PAT brings the opportunity to monitor and adjust the process very efficiently.

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