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Quality Control of Medical Food Using near Infrared Spectroscopy and Multivariate Calibration Models

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Abstract: Analytical methodologies were developed based on the near infrared spectroscopy (NIR) associated with chemometric tools to predict the content of macronutrients (total carbohydrate, total protein, and total lipids) in medical food. We prepared the samples employed in this study according to a mixture design with percentual variations from 25% to +25% of macronutrients. Partial least squares (PLS) regression models were built with 70 and 30 samples as calibration and validation sets, respectively. We chose the best processing techniques and results based on the parameters of the ASTM 1655 standard. The models were used to determine these macronutrients in marketed enteral nutrition products, of three different batches, that have quality certification. The average errors in the determination of total carbohydrate, total protein, and total lipids were 1.8, 4.3, and 2.3 %, respectively. The percentages of errors found in this study suggest that the developed model may be useful for the quality control laboratory routine.

Keywords: Medical food; NIRS; Quality control

1. INTRODUCTION

Enteral nutritional support is essential when oral feeding is not used. Enteral nutrition is recommended in cases of malnourished patients, who are momentarily or permanently unable to meet their biological needs by oral feeding. Usually, these patients are in critical clinical situations, such as victims of multiple traumas, patients in the postoperative period, affected by digestive diseases, strokes, or even premature newborns (ALHASHEMI; GHORBANI; VAZIN, 2019).

The marketed products of enteral nutrition are sources of several essential nutrients for the body, such as proteins, carbohydrates, fat, and vitamins, which simulate what would be the normal intake of these nutrients in the oral diet. This nutrition is characterized by providing a balanced diet, rich in nutrients. Usually, these products are presented in liquid or powder formulations. Currently, there are several companies specialized in the manufacture of enteral foods, in which there are also different formulations for different types of patients (JANSEN et al., 2017).

In Brazil, the enteral nutrition is subject to the regulations established by health surveillance, which advocate and establish quality standards for these foods, since their raw materials, storage, the composition of their products, up to the quantification of the percentages from each nutrient in their final composition (BRASIL, 2017).

Quantifying these nutrients in medical food has proved to be a challenge. There are specific methodologies, which are expensive, present high sample consumption, produce more waste, and, therefore, are not environmentally friendly. Thus, several industries in this field have been researching new technologies that can overcome these drawbacks.

An alternative technique that can successfully be employed for the determination of these components is the near infrared spectroscopy (NIR), which is an innovative technique in this segment, making it possible to create forecast models that can be used in the quantification of these nutrients.

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These forecasting models are developed employing chemometric tools, which allow to manipulate the spectral data to recognize some pattern among samples or to correlate them with parameters of interest (e.g. concentration of components) and extract the analytical information. This technology is well established as an alternative way to quality control of food and pharmaceuticals, as it is a relatively low-cost technique. In general, prior sample preparation is not required, with little or no use of chemical reagents, and, therefore, environmentally friendly. Another advantage of NIR spectroscopy is the time to acquire spectral data, on average 30 seconds per sample.

Recently, NIR spectroscopy has been employed to analyze cashew micro and macronutrients (SAMAMAD et al., 2018), in soybean quality control (MARCHESE et al., 2018), in the evaluation of contaminants (THANAVANICH, 2022) (THANAVANICH, 2022), in the determination of casein macropeptide in milk (OLIVEIRA et al., 2018), in the evaluation of flour texture (SILVA, 2022), among others. However, the application of NIR spectroscopy in enteral foods has not yet been explored, with only a few studies in the area of clinical nutrition. Therefore, this work presents a non-destructive analytical method, based on NIR spectroscopy and partial least squares regression models (PLS), to determine macronutrients in a type of commercialized enteral nutrition product.

2. MATERIALS AND METHODS

We conducted the research in an enteral products formulation industry, located in Fortaleza, Ceará, Brazil. We also chose this company's most commercialized product as our object of study. For ethical reasons, the product will not have its name disclosed in the research. In this study, the product was called Mix Enteral (ME).

2.1. Selection of Medical Food

ME is a powder (color: light yellow) and has been sold in cans with around 445 g of total mass. This enteral nutrition presents itself as a rich and complete diet, has a high concentration of proteins, and is also rich in immunomodulators that are important for strengthening the immune system. ME also has dietary fibers, which relieve constipation, prevent diarrhea, and contribute to the healthy maintenance of the normal intestinal microbiota (NUTERAL, 2018).

We chose this product because of its widespread commercialization, high complexity of its raw materials, and the variety of nutrient types that are originated from the 14 raw materials, which can be classified according to their molecular weight in macronutrients (Maltodextrin, Neofiber, Vanilla flavor, Potassium Acesulfame, Canola Oil, Sunflower Oil, Omega 3, Fatty Acids, Calcium Caseinate, Soy Protein Isolated, and Hydrolyzed Wheat Protein) and micronutrients (L-Arginine, L-Carnitine, L-Taurine, and Premix [a mixture of different vitamins and minerals]).

2.2. Samples

We prepared one hundred samples, according to a mixture design, with 100 g/each from the original (commercialized) composition of the ME (considered as midpoint). All macronutrients varied ± 25% from the midpoint.

All 100 samples were prepared using an experimental mixture design. The raw materials were weighed on an analytical balance (Edutec model EEQ9003F-B with an uncertainty of ± 0.0001 g) and added to a plastic container, where manual and systematic stirring was carried out over for 5 minutes. The determination of nutrient content was calculated by the centesimal ratio of the heavy mass of the raw materials and the total mass of the sample. For the calculations, we considered the purity degree declared in the reports of the raw materials.

2.3. Spectra Acquisition

Spectral data from 800 to 2500 nm were recorded by a Perkin Elmer Frontier NIR/MID equipment with an average of 32 scans and spectral resolution of 16 cm^{-1}, using a diffuse reflectance accessory. Before each analysis, a background spectrum of Teflon was recorded, and each sample was repacked and scanned three times for the average.

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2.4. Data Analysis and Software

This research carried out a study of pre-processing on the spectral data to build the calibration and prediction models. The first procedure performed was the Multiplicative Signal Correction (MSC), followed by the smoothing, which, according to Gris et al. (2017), are useful procedures to reduce light scattering and to decrease random noise. After this process, it was verified that the spectral region between 800 and 969 nm was noisy and without spectral information. Therefore, this spectral region was removed from the study, and the suitable spectral region was limited between 970 and 2500 nm. In addition, pre-processing strategies as Standard Normal Variation (SNV) and first derivative Savitsky-Golay in five-point windows were also investigated.

We applied Principal Component Analysis (PCA) to find out the reproducibility of samples with similar composition, prepared according to the mixture design. In addition, PCA was used to identify the variability of the composition around the studied product label and to verify which raw materials have the greatest influence on the similarity of the composition. The values of the nutrient concentration were self-scaled, and all spectral data were mean-centered before modeling procedures. Detection of outliers was made using residual scores versus leverage plots.

In the study, we built multivariate calibration models, based on Partial Least Squares (PLS) regression. This methodology becomes particularly important in NIR spectroscopy, where it is possible to manipulate associative spectral absorbance data in more than one frequency (wavenumber or wavelength) at the same time. In theory, multivariate calibration is useful to establish the relation of two matrices (**X** and **Y**), where **X** is the set of experimental data containing the independent variables and the dependent variables (**Y**) (CARVALHO, 2015; PASQUINI, 2003).

The multivariate calibration was performed following the guidelines of the international standards published in ASTM E1655. We grouped the samples into two sets: 70 samples for calibration and full cross validation (Leave-One-Out validation, including the minimum and maximum values of each nutrient studied and the samples of the central point) and 30 samples for external validation. The correlation coefficient (r), determination coefficient (R^2), root mean square error of cross validation and external validation (RMSECV and RMSEP, respectively), as well as the viability (bias) of the models were evaluated to verify the more robust and efficient calibration models.

The average error of the calibration and prediction-built models (RMSECV and RMSEP) were calculated using the following equations:

$$\mathrm{RMSECV} = \sqrt{\frac{1}{n_c}\sum_{i=1}^{n_c}(\hat{y}_i - y_i)^2}$$

and

$$\mathrm{RMSEP} = \sqrt{\frac{1}{n_p}\sum_{i=1}^{n_p}(\hat{y}_i - y_i)^2}$$

where $\hat{y}$ is the predicted value of the i^{th} sample in the calibration or prediction, y_i is the actual sample value provided by the reference method, n_c is the sample number in the calibration, and n_p is the sample number in the prediction.

We evaluated the models to verify the best correlation (r closest to 1), the determination coefficient (R^2 closest to 1), the lowest mean determination error (RMSECV and RMSEP closer to 0), and bias (closer to 0).

Models were checked for the highest performance in external validation, and they were used to predict nutrients in samples from three different batches of the product marketed by the company.

All calculations were performed employing the Unscrambler® X 10.4 (CAMO S.A, Oslo, Norway) software package.

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3. RESULTS AND DISCUSSION

3.1. Principal Component Analysis (PCA)

The preliminary study using PCA was performed with contents of the raw materials, in the 100 samples of mixture design, to check similar samples for nutrient concentration and evaluate the reproducibility of the replicates of the selected product (samples 98, 99, and 100).

Figure 1A shows the scores plot. The first principal component (PC-1) and the second principal component (PC-2) explain 37% and 20% of data variance, respectively. It is possible to notice the samples distributed in six large groups around the three samples of the central point (circled samples), which are replicates of selected enteral product.

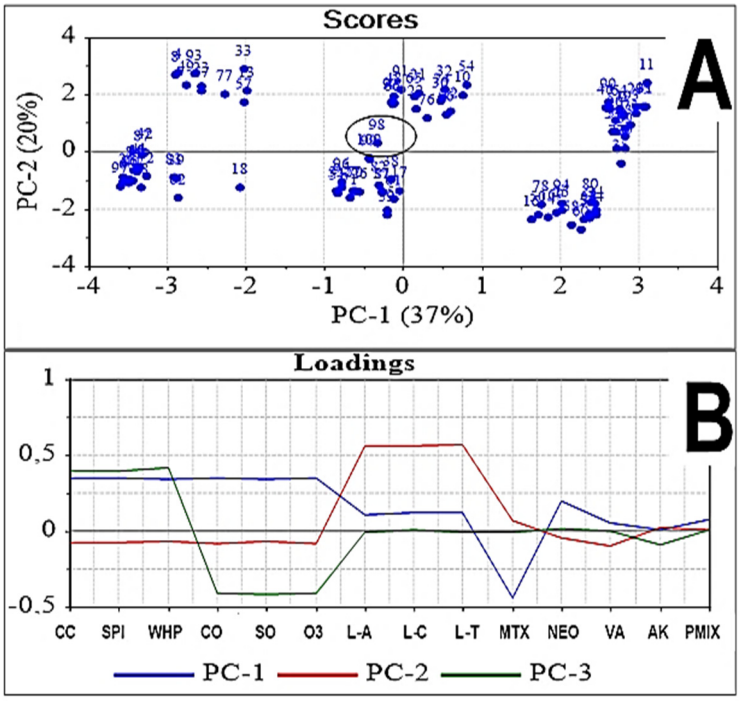

Figure 1. A - Scores plot (PC-1 and PC-2) for the contents of the raw materials in the 100 samples of the ME prepared according to the mixture design. B - Loadings from PC-1, PC-2, and PC-3 obtained from the concentrations of the 14 raw materials of the 100 samples of ME. CC (Calcium Caseinate); SPI (Soy Protein Isolated); WHP (Wheat Hydrolyzed Protein) CO (Canola Oil); SO (Sunflower Oil); O3 (Omega 3); L-A (L-Arginine); L-C (L-Carnitine); L-T (L-Taurine); MXT (Maltodextrin); NEO (Neofiber); VA (Vanilla flavor); AK (Potassium Acesulfame); PMIX (Premix).

The loadings plot (Figure 1B) shows the influence of the variables in the sample arrangements in the scores plot, where the PC-1 (blue line) represents the influence of maltodextrin, which is a carbohydrate in greater abundance in the ME. Therefore, it is possible to assume that PC-1 is represented by carbohydrates, also the samples that hold the greatest amounts of carbohydrates were displayed at the bottom (negative) of the scores plot.

PC-2 (red line) shows the influence of amino acids on samples. Despite the small amount of this micronutrient, this influence may arise from amino acids present in proteins. The samples that were influenced by this PC are displayed at the top (positive) of the scores plot.

PC-3 (green line) is not represented in the scores plot. However, this PC explained a large portion of the study (15%), and the loadings plot assumes that PC-3 is influenced by lipids. The characterization of the PCs is of paramount importance for better knowledge of the samples involved in the study, and the results obtained in the PCA are in accordance with the composition of the ME and its variations, confirming that the three nutrients in higher quantities in this enteral nutrition are respectively: carbohydrates, proteins, and lipids.

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3.2. Spectral Absorption Data in the Near Infrared and Pretreatments

Although it is not possible to observe the differences between the samples, it is possible to identify that the spectra showed a difference from the baseline, which can be attributed to light scattering, and it is not related to spectral information of sample contents (SOUZA; MADARI; GUIMARÃES, 2012). This light scattering can be corrected using pre-processing strategies, as shown in Figure 2.

Figure 2B shows the spectra without the wavelength range between 800–970 nm. The removed region was necessary due to the strong noise even after pre-treatments. It was also observed through the atlas of Workman and Weyer (2012) that this band did not present relevant information for the study. The particle size and the scattering effect imposed in the absorbance were compensated for by multiplicative scattering correction, as shown in Figure 2B. Other pre-treatments were also tested, such as SNV, which is similar to the spectra treated with MSC. However, according to Tibola et al. (2018), the SNV is more robust than the MSC, as it does not use the medium spectrum as a reference, thus making the detection of samples considered anomalous (outliers) more difficult.

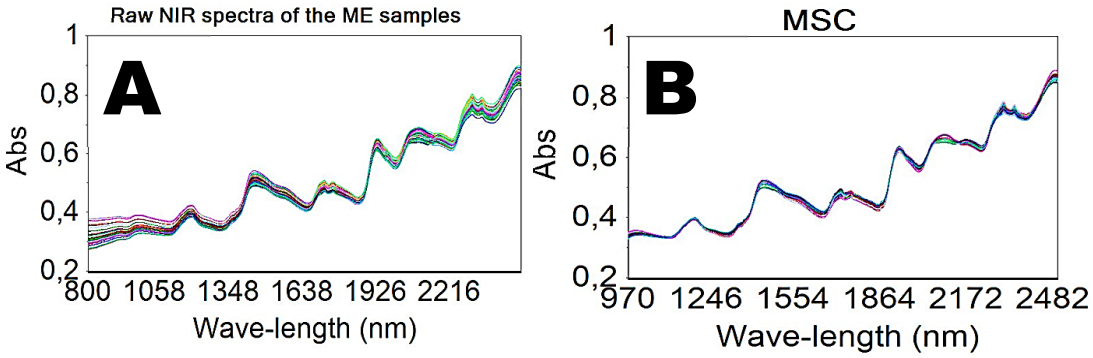

Figure 2. A – Raw NIR spectra (800–2500 nm) of the ME samples. B – MSC pretreated spectra of the ME samples in the wavelength range between 970 and 2500 nm.

After this procedure, it was applied the first derivative Savitzky-Golay in the pre-treated spectra by MSC, also in the pre-treated spectra by SNV. The first derivative spectra showed data noise and this may cause losses during the construction phase of the models. In such cases, the use of smoothing can be interesting.

The effects of Savitzky-Golay smoothing with 5 points in the 100 spectra were also tested with the first derivative Savitzky-Golay. The use of derivatives, according to Ferreira (2015), is recommended to correct a possible shift in the spectrum, which may be caused by the type of sample or even by some instrumental error. This type of displacement is common in diffuse reflectance spectra, and this problem can be solved with the application of the first derivative Savitzky-Golay.

3.3. Calibration Models and External Validation

Table 1 shows the results obtained for the PLS models built to macronutrient contents in the ME, varying the processing method, after correcting the systematic behaviors presented by the raw spectra.

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Table 1. Summary of statistics for the calibration and prediction sets for macronutrient contents using NIR and PLS model, with different spectral pre-processing. LVs: latent variables; RMSECV and RMSEP: root mean square error of cross validation and prediction, respectively; R2: coefficient of determination; MSC: multiplicative scatter correction. SNV: standard normal variate.

Nutrient	Calibration (n=68)					External validation (n=30)		
	Pre-processing	Range g. 100g^{-1}	R^2	RMSECV	LVs	R^2	RMSEP	Bias
total carbohydrate	MSC	38.1 – 62.9	0.996	0.618	4	0.996	0.7	0.111
total protein	SNV with 1st derivative	14.6 – 24.9	0.993	0.631	4	0.992	0.6	-0.004
total lipids	MSC	10.9 – 18.3	0.978	0.507	4	0.984	0.6	-0.033

We obtained the best performance for macronutrients using models that employed simpler pre-processing procedure, in general only with light scattering correction (MSC). It is worth to mention that some outliers (two or three samples) were identified and eliminated during the modeling procedures.

Urbano-Cuadrado et al. (2004) reported that calibration models with R^2 values higher than 0.900 indicate excellent precision, and between 0.700 and 0.900 mean that the model presents good precision. According to the authors, R^2 values less than 0.700 allow the analytical use of screening only, which allows the samples to be classified into low, medium, and high values. This classification is also widely used in the quality control of several industrialized products, mainly in the food industry. Considering this point of view, it is possible to verify that all macronutrient models showed excellent accuracy when analyzing the obtained R^2, in particular the models of total carbohydrates with MSC, SNV, and first derivative pre-processing, which presented $R^2 < 0.995$.

The calibration models for total proteins and lipids were classified as excellent, presenting R^2 above 0.900, including models without chemometric treatments. All macronutrients showed good statistical parameters, with $R^2 > 0.980$. The carbohydrate, protein, and total lipid models that were pre-treated with MSC proved to be similar to the models pre-treated with SNV with an $F = 0.9821$ test showing a 95% confidence level. These were the models that presented the best statistical results.

3.4. Forecast of Marketable Samples

The best PLS models were employed to predict the nutrients in commercial ME samples from three different batches (Lot A, Lot B, and Lot C). Three different samples were randomly chosen from each batch.

Firstly, a study was carried out to verify the similarity of the spectral behavior of the three industrialized medical food samples with those for the central point of the mixture design (98, 99, and 100) and samples with the smallest (sample 94) and the highest amount of carbohydrate (sample 97), as shown in Figure 8. As we can observe, spectra of industrialized samples are remarkably similar to those employed in the calibration set, which shows that the samples can be predicted by the developed PLS models.

The prediction results of ME macronutrients obtained for the commercial samples are presented in Table 2. The predictions of nutrient contents are consistent with the data provided by the product label, with an average error of ± 2.1% for macronutrients.

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Table 2. Results for macronutrients prediction of commercial samples of three different lots employing the PLS models. MAPE: mean absolute percentage error of prediction.

Nutrient	Samples	Lot A	Lot B	Lot C	MAPE (%)
Total carbohydrates g. 100g^{-1}	Sample 1	51.8 ± 1.0	53.8 ± 2.4	51.9 ± 2.2	1.8
	Sample 2	52.6 ± 1.0	53.7 ± 2.4	52.9 ± 2.1	
	Sample 3	53.7 ± 1.2	54.2 ± 2.4	53.6 ± 2.2	
Total proteins g. 100g^{-1}	Sample 1	20.4 ± 1.0	21.5 ± 1.4	20.4 ± 1.2	4.3
	Sample 2	18.0 ± 1.0	19.3 ± 1.3	19.4 ± 1.3	
	Sample 3	17.7 ± 1.0	19.3 ± 1.3	19.2 ± 1.2	
Total lipids g. 100g^{-1}	Sample 1	16.6 ± 3.1	14.2 ± 2.7	15.4 ± 2.1	2.3
	Sample 2	16.2 ± 3.0	14.2 ± 2.6	14.2 ± 2.2	
	Sample 3	16.3 ± 3.3	14.1 ± 2.5	14.1 ± 2.5	

The results of the table reveal the potentialities of using NIR for the quantification of food for enteral use, with its prediction error many times lower than the average errors obtained in the quantification of these nutrients by the reference method. This type of experiment, which is a pioneer in the study of the quality control of enteral foods, presents advantages regarding the use of the reference method, including speed, practicality, savings with reagents, non-generation of waste, and the possibility of commercialization of samples analyzed since these are not destroyed or processed and this has a positive impact on the industries in this segment.

4. CONCLUSIONS

Near infrared spectroscopy (NIR) associated with multivariate calibration models allowed the development of a reliable and efficient analytical method to determine the total carbohydrate, protein, and lipid contents in industrialized medical food. The results evidenced that it is possible to implement this technology in the industry for quality control of industrialized medical products. The developed method can bring benefits to companies by introducing in the production process a high-quality, fast, inexpensive, non-destructive quality control, without consuming chemical reagents, and environment-friendly.

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