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Quantification of the active ingredient in a pharmaceutical topical gel formulation

Abstract

This report demonstrates that Fourier transform near-infrared (FT-NIR) spectroscopy can be used for the quantitative characterization of an active ingredient in a translucent gel formulation. Gels were prepared with 0%, 1%, 2%, 4%, 6%, and 8% ketoprofen. These preparations were placed in disposable vials and analyzed with the Thermo Scientific™ Antaris™ FT-NIR Analyzer in the transmission module. The results demonstrate that for these formulations FT-NIR is a good alternative to other time-consuming analyses.

Introduction

Gels, creams, ointments, and other topical formulations represent a small but significant overall fraction of marketed pharmaceutical products. Most of these formulations present analytical challenges to those who must develop methods to test them. These products typically require tedious extractions and difficult sample preparation procedures.

Fourier transform near-infrared (FT-NIR) spectroscopy is an analytical technique that has gained popularity.[1-4] The major strengths of FT-NIR include fast and easy operation, good method accuracy and precision, and the ability to perform non-destructive analyses. However, the most attractive advantage of FT-NIR, with respect to the analysis of topical formulations, is that samples do not typically have to be manipulated prior to analysis.

FT-NIR has been used extensively in the pharmaceutical industry for the analysis of raw materials, intermediate products, and finished products.[1–4] Among the finished products most often subjected to FT-NIR analysis are tablets,[2–3] capsules, and lyophilized materials.[5] However, FT-NIR has seldom been investigated as a means for the routine analysis of topical formulations such as gels, creams, and ointments. This paper reports such an investigation for a clear gel formulation containing ketoprofen as the active ingredient.

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Drug (Ketoprofen)		Triethanolamine		Carbopol 980		Water		Propylene Glycol	
% (w/w)	Grams	% (w/w)	Grams	% (w/w)	Grams	% (w/w)	Grams	% (w/w)	Grams
0	0	8	2	1	0.25	45.5	11.375	45.5	11.375
1	0.25	8	2	1	0.25	45.0	11.250	45.0	11.250
2	0.50	8	2	1	0.25	44.5	11.125	44.5	11.125
4	1.00	8	2	1	0.25	43.5	10.875	43.5	10.875
6	1.50	8	2	1	0.25	42.5	10.625	42.5	10.625
8	2.00	8	2	1	0.25	41.5	10.375	41.5	10.375

Table 1. Composition of carbopol gel formulations

Experimental

Gel formulation preparation

Carbopol® 980 gels were formulated by first preparing a stock solution of the Carbopol (Noveon, Inc., Cleveland, Ohio) in distilled water and propylene glycol (Fisher Chemicals, Fairlawn, New Jersey). Specifically, 3.75 grams (g) of Carbopol were slowly added to a mixture of 118.125 g of water and 118.125 g of propylene glycol. The mixture was stirred slowly with a magnetic stirrer at 25 °C until all the Carbopol was dissolved.

Separately, appropriate quantities of ketoprofen (Hawkins Chemical, Minneapolis, Minnesota) were dissolved in a cosolvent (a mixture of water and propylene glycol) and triethanolamine (Spectrum Chemical, New Brunswick, New Jersey) to yield five different drug solutions (1%, 2%, 4%, 6%, and 8% drug content). Each drug solution was subsequently mixed with 16 g of Carbopol stock solution in a 50-ml beaker. The resulting mixtures were stirred slowly with a spatula until homogenous gels were formed. The gels were then transferred into clear glass vials and centrifuged at 1000- to 3000-rpm for up to 10 minutes to remove any entrapped air bubbles. A blank gel (no drug content) was also prepared by the above-mentioned procedure. The compositions of the formulations are shown in Table 1.

The structures of the formulation components are shown in Figure 1. The polymeric structure for Carbopol, an acrylic polymer, is shown in Figure 2. The purpose of the triethanolamine is to affect the desirable solution conformation of Carbopol. This leads to better consistency in the viscosity of the gels. The Carbopol confers the gelatinous properties to the formulations.

Mode of measurement	Transmission
Spectral range	4000 cm^{-1} – 10000 cm^{-1}
Resolution	4 cm^{-1}
Co-averaged scans	64
Data collection time	47 seconds
Detector	InGaAs

Table 2. Data collection parameters

Sample preparation

Samples were placed in 7-mm diameter disposable glass vials (Alltech Corporation) for analysis. The gels were loaded into the vials upon preparation, and the vials were centrifuged to remove air bubbles. Four aliquots of each formulation were transferred to separate vials to assess method reproducibility.

Data collection

Data were collected for these samples on an Antaris FT-NIR Analyzer. The transmission module (Figure 3) that is standard to the instrument was employed. The experiment was conducted under room temperature conditions (21 °C). The data collection parameters for this experiment are listed below in Table 2. The four vials from each formulation were analyzed individually.
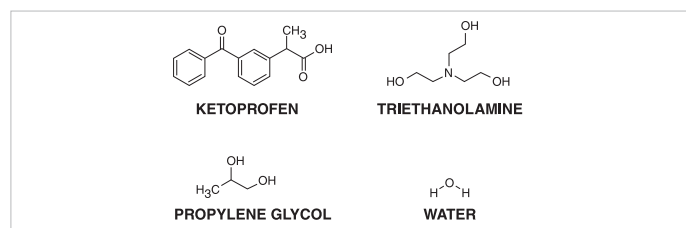

Figure 1. Structures of compounds in gel formulations
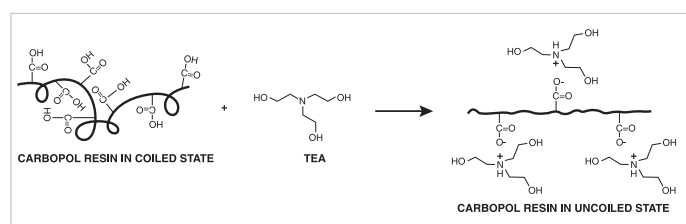

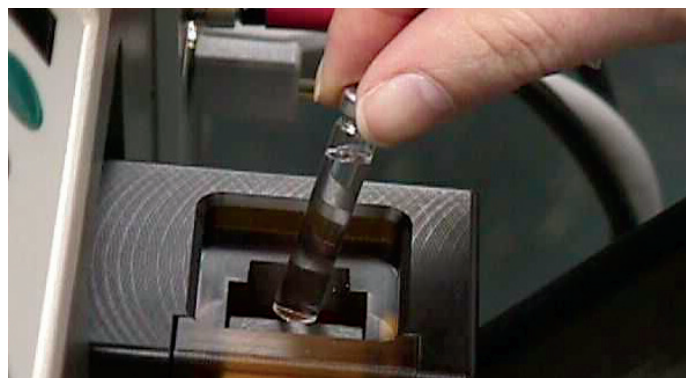Figure 2. Structure of carbopol in the presence of triethanolamine

Figure 3. Antaris transmission module

Chemometric modeling

All chemometric modeling was performed using our Thermo Scientific™ TQ Analyst™ Software. The Stepwise Multiple Linear Regression (SMLR) and Partial Least Squares (PLS-I) algorithms were used to derive calibration models. Data points for the SMLR models were selected based on the best correlation with the known ketoprofen quantities.

Predicted Residual Error Sum of Squares (PRESS) plots were used to select the appropriate number of PLS factors for each model. Multiplicative Scatter Correction (MSC),[6] Norris Derivatives,[7] and Savitzky-Golay[8] derivatives were generally used for pre-treatment.

Results and discussion

The spectrum for ketoprofen powder is shown in Figure 4. Clearly, ketoprofen has a strong FT-NIR signal with well-defined spectral features. The second derivative spectra of the formulations outlined in the Experimental section of this note are overlaid in Figure 5. Judging from these plots, sufficient spectral differences exist to allow quantitative characterization.
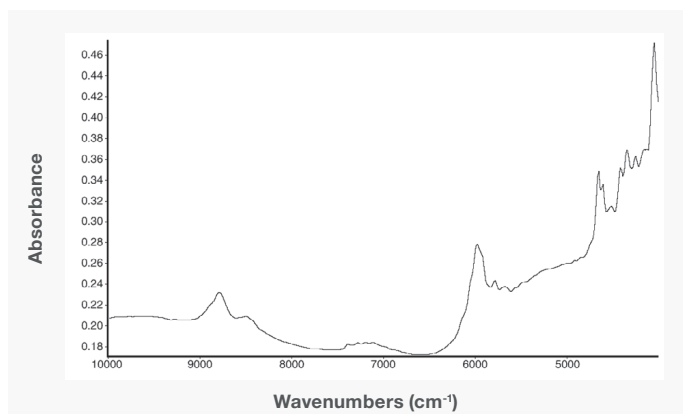

Figure 4. Unprocessed FT-NIR spectrum for ketoprofen raw material
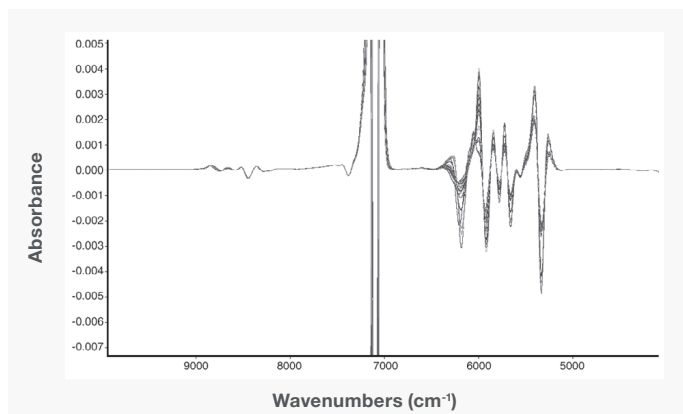

Figure 5. Full-range second derivative FT-NIR calibration spectra

Quantitative analyses

The data were subjected to multiple calibration models. The best model is reported. All of the sample data were placed in the calibration set except one sample each from the 1%, 4%, and 6% levels. A single-point SMLR model was chosen because it is simple and provides a straightforward assessment of feasibility for FT-NIR analysis of these formulations.

The spectral data point used for calibration was 8792 cm^{-1}. Figure 6 shows an expanded second derivative plot with spectra for all of the formulations overlaid at this point of interest. This frequency is in the area of the second C-H overtone for ketoprofen.

The calibration plot is shown in Figure 7. The correlation coefficient for this model was 0.9996. The Root Mean Squared Error of Calibration (RMSEC) was 0.0775%.
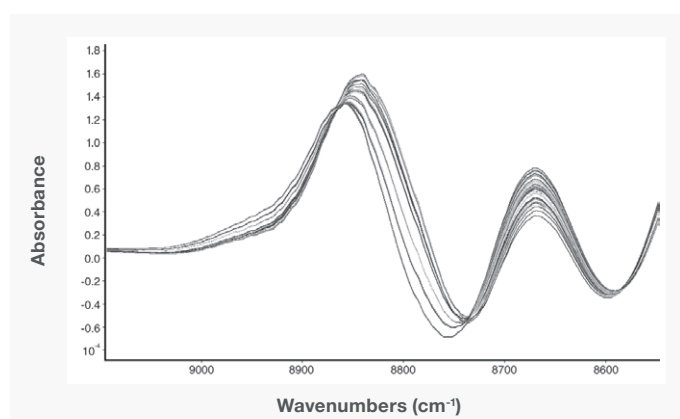

Figure 6. Overlay of expanded second derivative spectra in the area used for calibration
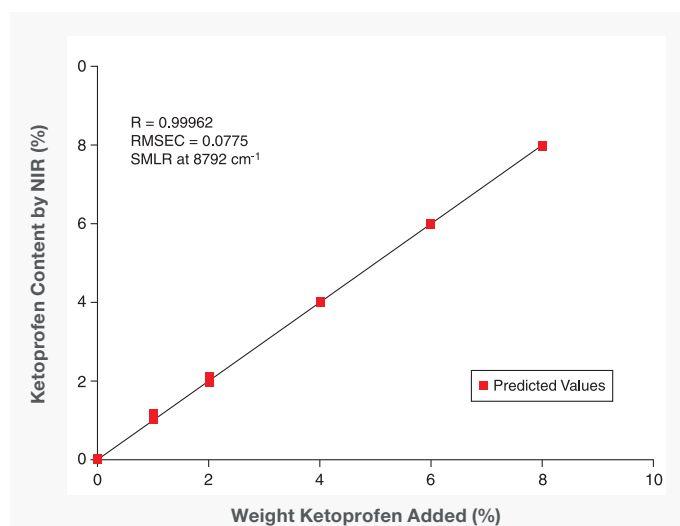

Figure 7. Calibration curve for ketoprofen content of gels

The quality of the calibration was assessed in two ways. The first was the use of the Root Mean Squared Error of Cross Validation (RMSECV) with a leave-one-level-out (all samples from one drug level) protocol. This allows reasonable evaluation of an initial calibration in the absence of a good validation sample set. For a good calibration, the RMSECV would be expected to be slightly higher than the RMSEC because one degree of freedom is taken away. This is the case for this calibration, as the RMSECV was found to be 0.0990%.

The second way in which the quality of the calibration was assessed involved the use of check samples left out of the calibration altogether. The calibration was applied to these samples, and the results are listed below.

Actual % ketoprofen content	Predicted % ketoprofen	% difference
1.00	1.00	0
4.00	4.02	0.55
6.00	5.98	-0.33

The sample for the 4% level was measured six times. The percent relative standard deviation (%RSD) of the six replicate measurements was 0.10%.

Conclusions

FT-NIR was applied to the analysis of a translucent topical gel formulation. The results suggest that FT-NIR transmission spectroscopy is an excellent means for the rapid and convenient analysis of these types of products. The error of this method is within that expected for pharmaceutical product assays.

The data were collected using an older model instrument Antaris FT-NIR. Currently, Thermo Scientific offers an improved model, the Antaris II FT-NIR, which offers superior speed and performance over its predecessor model.

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