Use of FT-NIR Transmission Spectroscopy for the Quantitative Analysis of an Active Ingredient in a Translucent Pharmaceutical Topical Gel Formulation

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ABSTRACT The objective of this study was to demonstrate the use of transmission Fourier transform near-infrared (FT-NIR) spectroscopy for quantitative analysis of an active ingredient in a translucent gel formulation. Gels were prepared using Carbopol 980 with 0%, 1%, 2%, 4%, 6%, and 8% ketoprofen and analyzed with an FT-NIR spectrophotometer operated in the transmission mode. The correlation coefficient of the calibration was 0.9996, and the root mean squared error of calibration was 0.0775%. The percent relative standard deviation for multiple measurements was 0.10%. The results prove that FT-NIR can be a good alternative to other, more time-consuming means of analysis for these types of formulations.

KEYWORDS: FT-NIR, Transmission Spectroscopy, Carbopol, Topical Formulations, Ketoprofen.

INTRODUCTION

Topical formulations, such as gels, creams, and ointments, 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. Typically, test procedures for these products require tedious extractions and difficult sample preparation procedures.

Fourier transform near-infrared (FT-NIR) spectroscopy is an analytical technique that has gained popularity in recent years for analyzing raw materials, intermediate products, and finished dosage forms¹⁻⁴. Among the finished products that have been most often analyzed using NIR spectroscopy are tablets^{2,3}, capsules, and lyophilized materials⁵. The major strengths of FT-NIR include fast and easy equipment operation, good accuracy and precision, and the potential to perform nondestructive 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 before analysis. A literature review showed that FT-

NIR has not often been used for routine analysis of topical formulations such as gels, creams, and ointments; hence, in this study, quantitative analysis of a clear topical gel formulation containing ketoprofen as the active ingredient was performed using transmission FT-NIR. Carbopol 980 gel was selected for this study because of its wide use as a topical gel in commercial formulations^{6,7}.

MATERIALS AND METHODS

Gel Formulation Preparation

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

Separately, appropriate quantities of ketoprofen (Hawkins Chemical, Minneapolis, MN) were dissolved in a cosolvent (a mixture of water and propylene glycol) and triethanolamine (Spectrum Chemical, New Brunswick, NJ) to yield 5 different drug solutions (with 1%, 2%, 4%, 6%, and 8% drug content). Each drug solution was subsequently mixed with 16 g Carbopol 980 stock solution in a 50-mL beaker. The resulting mixtures were stirred slowly with a spatula until homogeneous 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 (with no ketoprofen) was also prepared by the above-mentioned procedure. The compositions of these formulations are shown in **Table 1**.

The structures of the formulation components are shown in **Figure 1**. The polymeric structure of Carbopol is shown in **Figure 2**.

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Table 1. Composition of Carbopol Gel Formulations

Drug (Ketoprofen)		Triethanolamine		Carbopol 980		Water		Propylene Glycol	
% (wt/wt)	Grams	% (wt/wt)	Grams	% (wt/wt)	Grams	% (wt/wt)	Grams	% (wt/wt)	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

Figure 1. Structures of compounds in gel formulations. **Figure 2. Structure of Carbopol in the presence of triethanolamine.** **Figure 3. Transmission experiment on the Antaris Fourier transform near-infrared instrument.**

Sample Preparation

Samples were placed in 7-mm-diameter disposable glass vials (Alltech Corp, Deerfield, IL) 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 from the samples using an Antaris FT-NIR analyzer (Method Development Sampling System, Thermo Nicolet Corp, Madison, WI) at room temperature. The transmission module (Figure 3) standard to the instrument was employed in this study. The data collection parameters for this experiment are listed in Table 2. The 4 vials from each formulation were analyzed individually.

Table 2. Data Collection Parameters Used

Mode of Measurement	Transmittance
Spectral Range	4000 cm^{-1} to 10 000 cm^{-1}
Resolution	4 cm^{-1}
Coaveraged Scans	64
Data Collection Time	47 seconds
Apodization	Norton-Beer medium
Detector	InGaAs*

* Denotes Indium Gallium Arsenide detector

Chemometric Modeling

All chemometric modeling was performed using TQ Analyst software (Thermo Nicolet Corp). Principally, 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 on the basis of the best correlation with the known ketoprofen quantities. Predicted residual error sum of squares plots were used to select the appropriate number of PLS factors for each model. Multiplicative scatter correction, Norris derivatives⁸, and Savitzky-Golay (S-G) derivatives⁹ were generally used for pretreatment.

RESULTS

The spectrum for ketoprofen is shown in **Figure 4**. It is clear from the figure that ketoprofen has a strong NIR signal. The second derivative spectra of the formulations outlined in the experimental section are overlaid in **Figure 5**. The area of interest for calibration is highlighted in **Figure 5**.

Quantitative Analyses

Many calibration models were generated from the data. All the sample data (except for 1 sample each from formulations containing 1%, 4%, and 6% wt/wt ketoprofen) were used to generate the calibration model. 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 results of the better calibration models for this data set are shown in **Table 3**. The model that was generated using the S-G derivative with a 25-point segment gave the best correlation and calibration error; however, the model constructed using the Norris derivative with a 25-point segment yielded similarly good results. Hence, the latter model is reported as the best one for this data set because the measurement precision for 6 replicate samples was significantly better (0.10% versus 0.55% for the S-G model).

Figure 4. Unprocessed Fourier transform near-infrared spectrum for ketoprofen raw material.

Figure 5. Full-range second derivative Fourier transform near-infrared calibration spectra.

The spectral data point used for calibration was 8792 cm^{-1} . **Figure 6** shows an expanded second derivative plot with averaged spectra for all of the formulations overlaid at this point of interest. This frequency is in the area of the second C-Hovertone for ketoprofen. It was necessary to use this region because the long pathlength employed in this experiment caused the first overtone region to absorb beyond the linear range of the response of the detector.

The calibration plot is shown in **Figure 7**. The correlation coefficient for this model was 0.9996, and the root mean squared error of calibration was 0.0775%.

Table 3. Results of Various Calibration Models for Topical Gel Formulations

Type of Calibration	Type of Derivative	Derivative Segment	MSC	Details	Correlation Coefficient (R Value)	RMSEC (%)
SMLR	Norris	25	No	8792 cm ⁻¹	0.9996	0.0775
SMLR	Norris	15	No	8798 cm ⁻¹	0.9996	0.0836
SMLR	Norris	5	No	8805 cm ⁻¹	0.9975	0.200
SMLR	S-G*	25	No	8776 cm ⁻¹	0.9998	0.0616
SMLR	S-G*	15	No	8780 cm ⁻¹	0.9987	0.141
SMLR	S-G*	7	No	8830 cm ⁻¹	0.9844	0.495
SMLR	S-G*	25	Yes	8776 cm ⁻¹	0.9995	0.0851
SMLR	Norris	25	Yes	8776 cm ⁻¹	0.9994	0.0955
PLS	None	None	Yes	3 factors; 7500-9500 cm ⁻¹	0.9929	0.335
PLS	S-G*	25	No	2 factors; 7500-9500 cm ⁻¹	0.9994	0.0948
PLS	Norris	25	No	2 factors; 7500-9500 cm ⁻¹	0.9995	0.0906

*S-G indicates Savitzky-Golay second derivative using a third-order polynomial.

MSC = multiplicative scatter correction; RMSEC = root mean squared error of calibration; SMLR = stepwise multiple linear regression; PLS = partial least squares.

Table 4. Predicted Ketoprofen Composition of Carbopol Gel Formulations

Actual Ketoprofen Content (%)	Predicted Ketoprofen Content (%)	Difference Between Actual and Predicted Ketoprofen Content (%)
1.00	1.00	0
4.00	4.02	0.50
6.00	5.98	-0.33

Figure 6. Expanded overlay for the averaged second derivative spectra of the area used for calibration. R indicates correlation coefficient; RMSEC, root mean squared error of calibration; RESECV, root mean squared error of cross validation; SMLR, stepwise multiple linear regression.

Figure 7. Calibration curve for ketoprofen content of gels.

The robustness of the calibration model was assessed in 2 ways: In the first assessment, all samples from 1 drug concentration were left out and the root mean squared error of cross validation (RMSECV) was calculated. The RMSECV for the calibration model was 0.0990%. The samples that were left out served as the validation samples for the calibration model. In the second assessment, the robustness of the calibration model was evaluated by leaving out one sample of 1%, 4%, and 6% ketoprofen and using them as the test samples. The calibration model was applied to these test samples; the results are listed in **Table 4**. The sample containing 4% ketoprofen was measured 6 times to test method precision. The percent relative standard deviation of the 6 replicates for this sample was 0.10%.

CONCLUSION

FT-NIR transmission spectroscopic technique was used to determine the drug content of a translucent topical gel formulation. The results suggested that FT-NIR transmission spectroscopy is an excellent analytical technique for rapid and convenient analysis of these types of products. The error of this method is within that expected for pharmaceutical product assays.

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