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Journal of Pharmaceutical and Biomedical Analysis
33 (2003) 21–32
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Use of near-infrared spectrometry for quantitative determinations of selamectin and moisture in topical formulations

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Received 13 August 2002; accepted 10 January 2003

Abstract

A rapid near-infrared spectrometric (NIR) method was qualified for use with the quantitative analysis of selamectin and moisture in topical formulations. Selamectin is currently marketed as a pet endectocide and is available in several formulations for cats and dogs. The use of NIR in this investigation replaces the in-process testing by liquid chromatography and concurrently provided moisture content that would otherwise only be available with additional Karl Fischer titration investigations. A seven-factor partial least square regression (PLS) of the second derivative spectra encompassing the wavelength region of 1450–2200 nm was used to quantify both selamectin and moisture content. A second three-factor PLS solely for water content was also applied and compared with the full model. This qualification confirms that this method may be used to quantitate selamectin and moisture as a process tool or to examine finished good samples. Each sample can be rapidly analyzed within 5 min on the current bench top system.

Keywords: Near infrared spectrometry; Selamectin; Moisture analysis

1. Introduction

Selamectin is a novel pet endectocide marketed as topical formulations (solutions intended for transdermal application) under the trade names of Revolution® and Stronghold®. These products are proprietary formulations at 60 and 120 mg/ml selamectin based on the type and weight of the pet. Selamectin is produced using a combination of biological and chemical synthesis schemes yielding an avermectin with unique properties that enable

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0731-7085/03/$ - see front matter
doi:10.1016/S0731-7085(03)00341-8

the product to effectively prevent heartworm while simultaneously act to prevent flea infestation [1,2]. Unlike Advantage®, selamectin is a drug product (not insecticide) and requires production under GMP guidelines.

GMP production requires established control of the topical formulation. Currently, the in-process testing for this process consists of time consuming chromatographic and titration methods. Selamectin has a strong chromophore and unique structure from the matrix. Though a proprietary chromatographic determination for selamectin is used, other chromatographic methods can be found in the literature [3,4]. With near-infrared spectrometric (NIR) rapidly becoming a pharmaceutical analysis tool of choice for rapid, nondestructive and process investigations [5–7], the technique was applied to the drug product formulation in order to reduce analysis times as well as investigate the potential for an in-line determination. Unlike the current procedures, NIR allows simultaneous determination of potency and moisture, an additional efficiency.

The NIR method was qualified for use with the quantitative analysis of selamectin and moisture in topical formulations. The use of NIR in this investigation replaces the in-process testing by liquid chromatography and concurrently provided moisture content that would otherwise only be available with additional Karl Fischer titration investigations. Because the structure of selamectin is unique to the product matrix, a unique chromophore was initially sought for NIR. However, no such unique assignment was found and chemometric tools were needed to distinguish CH overtones from the drug and formulation matrix. After a second derivative manipulation of the spectral scans, a seven-factor partial least square regression (PLS) of the second derivative spectra was used to quantify both selamectin and moisture content. An additional three-factor PLS solely for water content was also applied and compared with the full model. The goal of this study is to confirm that NIR spectrometry may be used as an effective tool to quantitate selamectin and moisture in-process and finished good samples.

2. Experimental

2.1. Near-infrared spectrometry

The NIR data reported was generated using Model 6500 NIR spectrometer (Foss NIR Systems, Eden Prairie, MN) equipped with a transmittance sample transport module and a heated cell holder set to maintain a temperature of 30 °C. The spectra were collected using a quartz cell (Foss NIR Systems, NR-7063-2, 2 mm path length) over a wavelength range of 400–2500 nm. The operation of the instrument, as well as the collection and subsequent manipulation of the spectra, was controlled using DELIGHT version 2.3a and DSQUARED version 1.2a software from Dsquared Development (LaGrande, OR).

2.2. Moisture determinations

The constituent values for the calibration set were generated using Metrohm Karl Fischer Coulometer Model 756 with Pump/Stirrer Model 703 (Brinkmann Instruments, Westbury, NY) equipped with a double platinum wire electrode (Brinkman Instruments, 6.0431.100). Hydranol Coulomat AG (Sigma-Aldrich, Milwaukee, WI) was used as a titrant and the suitability of the instrument was confirmed using a 1000 μg/g Aquastar Water Check Solution from EM Science (Gibbstown, NJ).

The moisture content for in-process and finished good samples was generated using Model 665 Dosimate with a Model 658 Karl Fischer processor (Brinkmann Instruments) equipped with a double platinum wire electrode (Brinkman Instruments, 6.0338.100). Hydranol Composite 2 (Sigma-Aldrich) was used as a titrant and the suitability of the instrument was confirmed using a Hydranol standard tartrate-2 hydrate standard at 15.66% (Sigma-Aldrich).

2.3. Liquid chromatography

The LC data reported was generated using a proprietary method on a Waters Alliance 2690 Module equipped with a Waters 2487 UV detector.

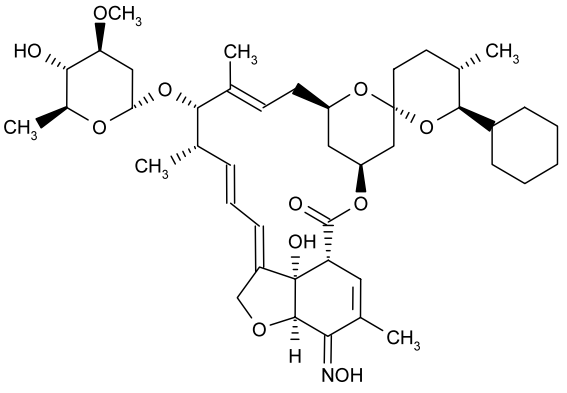

Fig. 1. Selamectin.

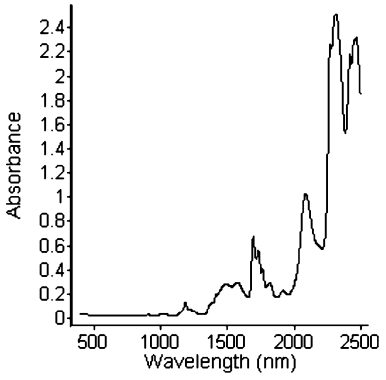

Fig. 2. NIR spectrum of selamectin in diluent.

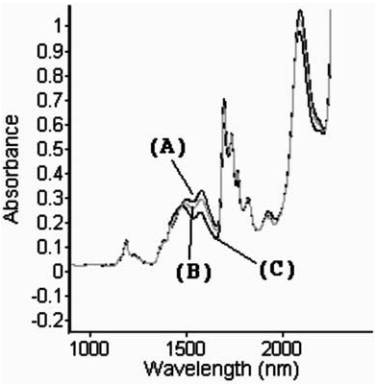

Fig. 3. NIR spectrum of (A) selamectin in diluent, (B) topical formulation placebo, (C) 12% topical formulation.

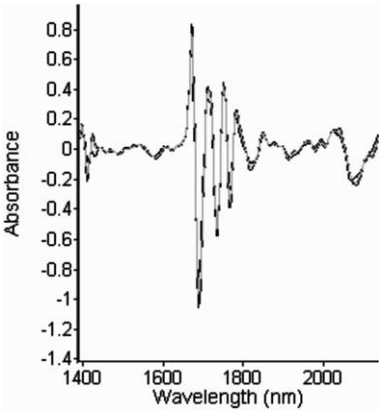

Fig. 4. NIR second derivative spectrum A–C in Fig. 1.

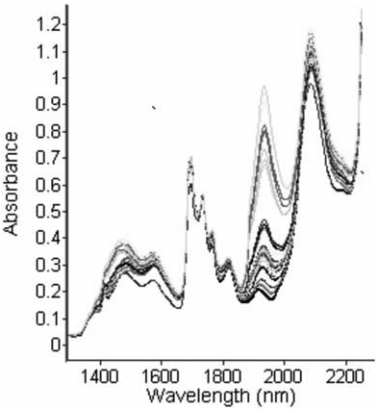

Fig. 5. NIR spectra of the calibration set.

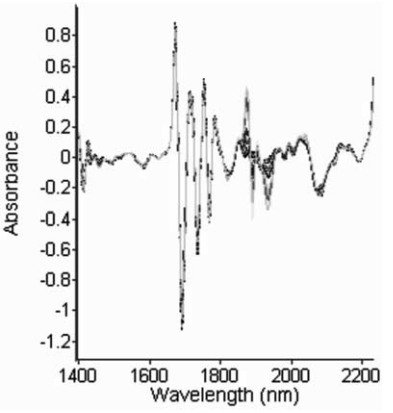

Fig. 6. Second derivative spectra of the calibration set.

Table 1
Accuracy of NIR model for selamectin

Sample (%)	Claim (mg/ml)	HPLC (mg/ml)	NIR (mg/ml)	LC (% claim)	NIR (% claim)
1-12	120.0	117.6	116.3	98.0	96.9
2-12	96.0	94.3	94.5	98.2	98.5
3-12	105.6	106.3	106.5	100.7	100.9
4-12	115.2	116.5	115.2	101.1	100.0
5-12	124.8	127.3	124.1	102.0	99.5
6-12	134.4	135.8	133.3	101.0	99.1
7-12	144.0	145.5	141.5	101.1	98.3
8-12	96.0	98.8	99.5	102.9	103.7
9-12	105.6	107.7	107.2	102.0	101.5
10-12	115.2	119.9	118.8	104.1	103.1
11-12	124.8	127.1	125.4	101.8	100.5
12-12	134.4	134.7	132.4	100.2	98.5
13-12	144.0	145.8	140.5	101.2	97.6
14-12	120.0	121.3	120.3	101.1	100.3
15-12	96.0	96.8	97.1	100.9	101.2
16A-12	105.6	108.4	107.2	102.6	101.5
17-12	115.2	115.3	113.9	100.1	98.9
18-12	124.8	126.9	124.8	101.7	100.0
19-12	134.4	134.3	131.9	99.9	98.1
20-12	144.0	143.9	140.2	99.9	97.3
21-12	96.0	98.5	96.3	102.6	100.3
22-12	105.6	102.9	102.6	97.4	97.2
23-12	115.2	116.2	113.3	100.9	98.3
24-12	124.8	128.6	122.5	103.1	98.2
25-12	134.4	133.7	128.4	99.5	95.5
26-12	144.0	145.0	138.0	100.7	95.8
27-12	120.0	119.6	114.6	99.6	95.5
28-12	96.0	98.6	94.8	102.7	98.8
29-12	105.6	107.4	102.5	101.7	97.1
30-12	115.2	116.0	111.1	100.7	96.5
31-12	124.8	124.5	123.9	99.8	99.3
32-12	134.4	136.0	134.3	101.2	99.9
33-12	144.0	144.9	141.6	100.6	98.3
34-12	96.0	96.6	97.9	100.6	101.9
35-12	105.6	105.2	106.3	99.6	100.6
36-12	115.2	117.3	116.9	101.8	101.5
37-12	124.8	126.2	125.3	101.1	100.4
38-12	134.4	135.4	133.9	100.8	99.6
39-12	144.0	144.5	142.9	100.4	99.2
40-12	120.0	124.3	123.0	103.6	102.5

2.4. NIR library sample preparation

Library samples were prepared based on proprietary formulations of selamectin topical products marketed at 60 and 120 mg/ml. As listed in the product MSDS, the formulation contains butylhdroxytoluene, dipropylene glycol methyl ether, selamectin and isopropanol. All materials used met the NADA requirements for these products. The samples and standards used for this study were produced or obtained from Pfizer (Lee's Summit, MO). The library used covered approximately 50–120% of the nominal concentration range of the topical formulation.

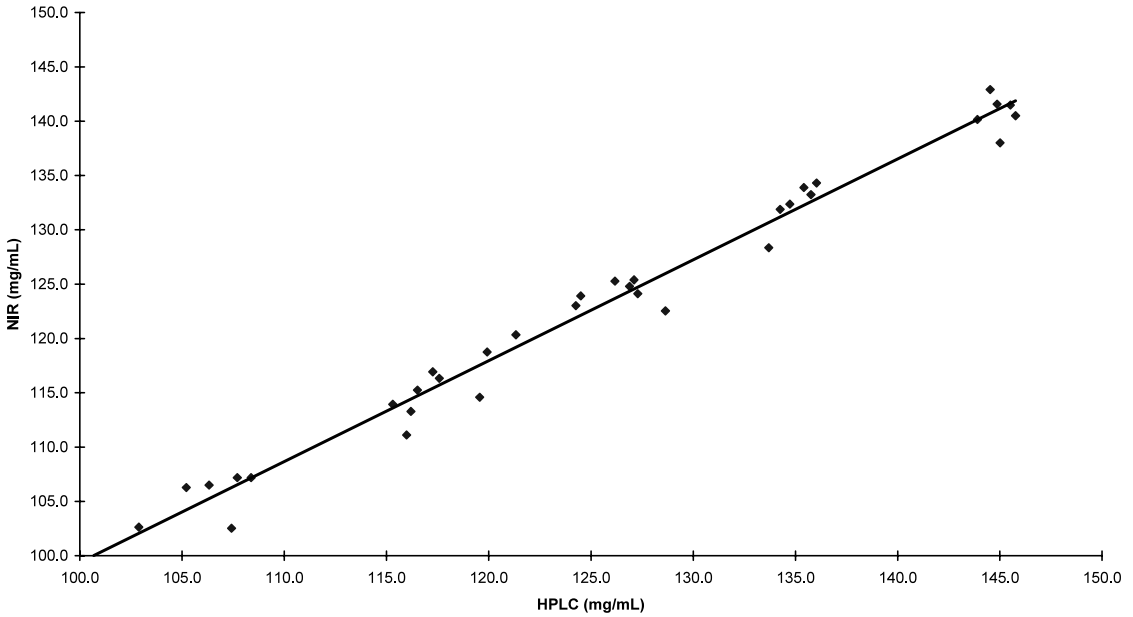

Fig. 7. Predicted NIR vs. liquid chromatographic result for selamectin.

3. Results and discussion

3.1. Specificity

The challenge of this particular NIR application was to ensure that a NIR response from selamectin could be resolved from a similar response that is produced from the product matrix. As seen in Fig. 1, selamectin has many unique opportunities to distinguish itself structurally from the matrix. Yet, as seen in Figs. 2–4, in the NIR region selamectin does not uniquely distinguish itself from the formulation matrix via a unique or characteristic wavelength response. Basically, the NIR has to distinguish the C–H NIR response of selamectin from the C–H response from several matrix sources! Even when the spectra were manipulated to form a series of second derivative spectra, as seen in Fig. 4, selamectin does not easily distinguish itself.

At this point, the data was challenged to verify if the slight change not only in wavelength response but also of the slopes of the response could be used to distinguish selamectin concentration. The study focused on preparing several library formulations that varied the individual matrix formulation components. An 80–120% variation of the nominal 60 mg/ml topical formulation range was used to stay within typical ICH parameters. [8] The series was then tested with a PLSs algorithm to model the selamectin and matrix response. [9] The PLS algorithm effectively distinguished between varying selamectin concentrations and the remainder of the formulation matrix.

The ability to monitor moisture content for the spectral window from 1800 to 2100 nm is routinely used in NIR with little interference and, thus, of less concern with this study. However, in order to see if this select region was more accurate than the full model developed for selamectin and moisture content, this individual model (“HOH”) for moisture content was examined to study the effectiveness of NIR to quantify moisture in the topical formulations.

3.2. NIR library

3.2.1. Preparation

In order to validate the NIR model for the effect of different component concentrations in the product matrix, several variations of the laboratory formulations were prepared. The variations

Table 2
Precision of NIR model for selamectin

Sample	Selamectin		Day 2 (% recovery)
	Day 1	Day 2	
Matrix 8	41.4	42.6	102.7
Matrix 9	41.3	43.1	104.4
Matrix 9	42.3	43.0	101.8
Matrix 10	41.6	42.3	101.7
Matrix 15	41.5	41.8	100.8
Matrix 11	42.9	42.7	99.4
Matrix 12	41.7	42.1	101.0
SEL 8	33.8	35.1	104.0
SEL 9	38.0	38.8	102.3
SEL 9	37.7	39.9	105.8
SEL 10	42.1	42.5	101.0
SEL 15	44.2	45.5	102.9
SEL 11	45.4	47.3	104.2
SEL 12	48.2	51.4	106.6
H_2O 1	28.6	30.3	105.8
H_2O 2	29.8	31.9	106.9
H_2O 3	29.6	31.4	106.2
H_2O 4	30.3	32.1	105.9
H_2O 5	29.7	30.9	104.1
H_2O 6	31.3	31.5	100.7
H_2O 7	29.8	29.6	99.2
H_2O 8	54.1	54.5	100.8
H_2O 9	55.8	57.5	103.1
H_2O 10	56.8	57.7	101.6
H_2O 11	56.2	57.7	102.6
H_2O 12	55.5	56.2	101.3
H_2O 13	55.7	58.1	104.4
H_2O 14	56.3	57.4	101.9

encompassed at least 80–120% of the nominal concentration range for topical products and were developed by spiking isopropanol with stock solutions of each of the matrix components. Each formulation was assayed by liquid chromatography to confirm selamectin and by Karl Fischer titration for moisture content. The final library was developed based on the historical development of the project: (a) the initial feasibility of NIR quantitation was based on a 28 laboratory solution library solely for the 60 mg/ml product formulation, (b) an additional series of 18 calibration set and 42 challenge samples based on the 120 mg/ml formulation were then produced and finally (c) the combined NIR model using the original 60 and 120 mg/ml library formulations.

3.2.2. NIR regions of interest

Through examination of the spectra and earlier work in our laboratory, the NIR model for combined selamectin and moisture determination used the spectral response from 1450 to 2200 nm that contains the first CH and OH overtones.

A second model solely for moisture determination was developed using the spectral response from 1800 to 2050 nm and focuses on the combination band for water. Figs. 5 and 6 illustrate the NIR response and second derivative series for the laboratory solutions used to development the NIR model library.

3.2.3. Derivatives and part least squares regression analysis

In Figs. 4 and 6 the spectra were operated on to form 13 point, second derivative spectra using the Savitzky–Golay algorithm. Using the derivative series, the spectra were further manipulated with the application of a seven-factor PLS algorithm. The algorithm was applied using the calibration library characterized with the LC results for selamectin, coulometric Karl Fischer results for moisture and the formulation value of the matrices' largest additive component. This third parameter was added to account for the matrix effects upon the selamectin response and to negate these effects in the PLS algorithm, a "dummy variable" if you will.

The HOH model was formed solely for moisture content determination. A three-factor PLS was used since the region was free from spectral interferences.

3.2.4. Liquid chromatographic analysis/NIR qualification

Forty laboratory blends of varying selamectin and matrix content were analyzed and the results given in Table 1. The lab blends all centered on a 120 mg/ml selamectin topical formulation. The data confirms the NIR is providing equivalent accuracy for selamectin as compared with both the theoretical and liquid chromatographic (Fig. 7) claim for selamectin content. As suggested by Bolton [10], a simple regression applied to the NIR and LC results yields a correlation of 0.993, a slope of 0.93 and an intercept of 6.5. At 95%

Table 3
Accuracy of NIR models for moisture

Sample (%)	KF (%)	NIR-full model (%)	NIR-HOH model (%)	NIR-full (% KF)	NIR-HOH (% KF)
1-12	0.66	0.64	0.62	97.5	94.1
2-12	0.75	0.76	0.76	101.1	100.2
3-12	0.70	0.70	0.69	99.1	97.6
4-12	0.60	0.59	0.56	98.5	93.2
5-12	0.72	0.71	0.68	98.6	94.9
6-12	0.56	0.54	0.51	96.4	91.3
7-12	0.61	0.59	0.55	96.8	90.9
8-12	0.61	0.60	0.58	99.1	96.3
9-12	0.70	0.70	0.69	99.9	98.9
10-12	0.58	0.57	0.54	98.8	93.8
11-12	0.73	0.72	0.70	98.1	95.5
12-12	0.67	0.65	0.62	96.8	92.3
13-12	0.65	0.64	0.60	98.2	92.9
14-12	0.68	0.67	0.65	98.2	95.6
15-12	0.52	0.51	0.48	98.2	91.4
16A-12	0.55	0.47	0.47	86.4	86.6
17-12	0.59	0.49	0.52	82.7	88.2
18-12	0.65	0.55	0.60	85.3	92.2
19-12	0.68	0.56	0.60	83.0	88.0
20-12	0.58	0.47	0.50	81.3	86.6
21-12	0.59	0.48	0.52	82.2	88.1
22-12	0.68	0.55	0.59	81.9	87.6
23-12	0.67	0.55	0.60	81.7	88.2
24-12	0.67	0.56	0.61	83.1	91.5
25-12	0.60	0.50	0.54	82.5	89.8
26-12	0.61	0.49	0.53	81.3	87.8
27-12	0.62	0.51	0.55	82.4	89.2
28-12	0.61	0.50	0.54	82.5	87.8
29-12	0.51	0.42	0.44	82.1	85.8
30-12	0.66	0.54	0.58	82.8	87.8
31-12	0.61	0.60	0.57	97.4	93.4
32-12	0.61	0.60	0.59	98.3	95.9
33-12	0.56	0.55	0.52	97.8	93.0
34-12	0.52	0.51	0.47	99.0	89.7
35-12	0.49	0.48	0.45	98.5	91.0
36-12	0.63	0.62	0.61	98.4	95.8
37-12	0.55	0.53	0.49	97.5	89.8
38-12	0.60	0.58	0.55	97.2	92.2
39-12	0.66	0.65	0.64	98.7	96.9
40-12	0.73	0.71	0.70	97.9	95.8

confidence, the t-test for the slope, the F-test for the slope and the confidence interval for the slope all conclude that a significant relationship exists between [1] the NIR result and the LC result and [2] the NIR result and the sample claim.

A portion of the library from approximately 50 to 120% of a 60 mg/ml selamectin topical formulation was repeated on a second day to illustrate precision. (Table 2) The simple regression applied to the NIR results yields a correlation of 0.997, a slope of 1.01 and an intercept of 0.98. At 95% confidence, the t-test for the slope, the F-test for the slope as well as the confidence interval for the slope all conclude that a significant relationship exists between the day 1 and day 2 NIR results for these samples.

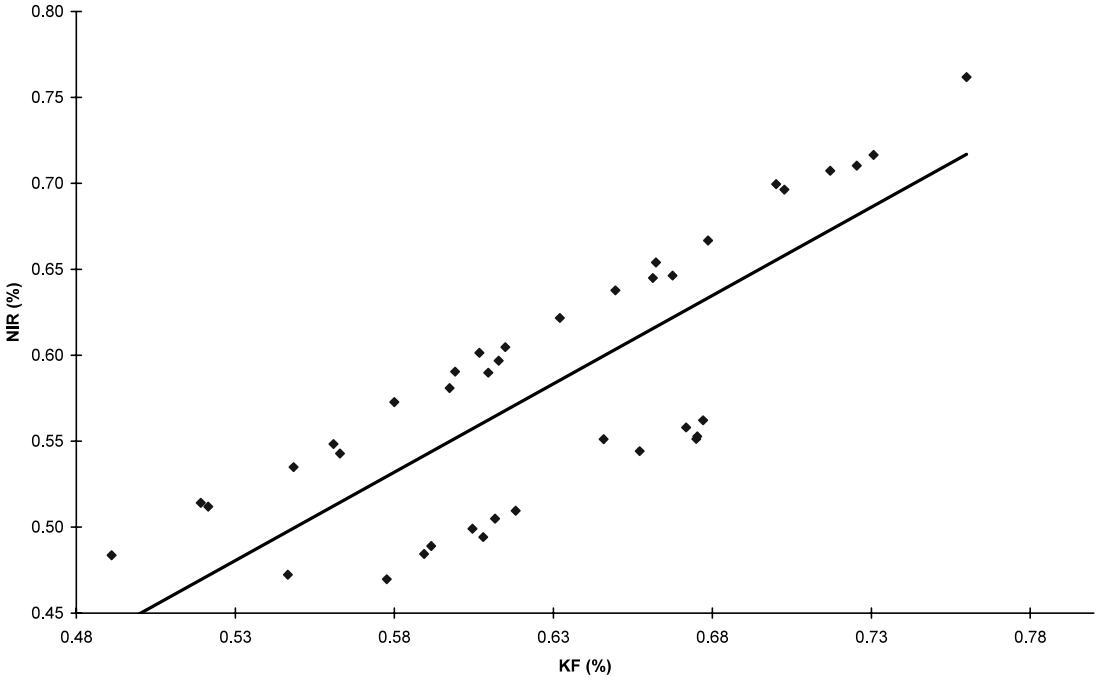

Fig. 8. Predicted moisture vs. KF titration result using the full NIR model.

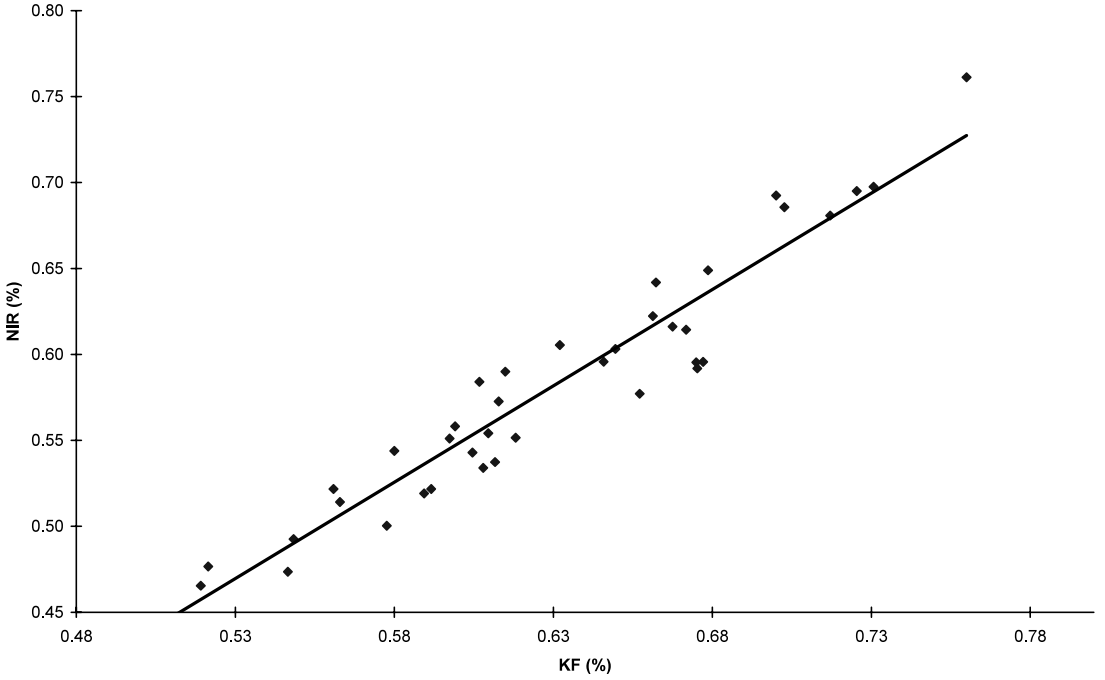

Fig. 9. Predicted moisture vs. KF titration result using the NIR HOH model.

Table 4
Precision of NIR models for moisture.

Sample	NIR full model		Day 2 (% recovery)	NIR HOH model		Day 2 (% recovery)
	Day 1	Day 2		Day 1	Day 2	
Matrix 8	0.39	0.40	100.6	0.38	0.40	103.7
Matrix 9	0.41	0.39	96.1	0.39	0.39	98.6
Matrix 9	0.46	0.45	98.7	0.45	0.45	100.2
Matrix 10	0.41	0.41	101.1	0.39	0.40	102.9
Matrix 15	0.40	0.42	103.1	0.38	0.40	105.0
Matrix 11	0.41	0.40	98.7	0.39	0.39	98.9
Matrix 12	0.40	0.40	99.9	0.37	0.38	101.2
SEL 8	0.42	0.41	97.5	0.40	0.40	99.6
SEL 9	0.41	0.40	97.6	0.40	0.39	98.5
SEL 9	0.40	0.41	100.9	0.38	0.40	103.5
SEL 10	0.39	0.40	102.9	0.37	0.39	105.0
SEL 15	0.40	0.40	100.8	0.38	0.39	102.7
SEL 11	0.40	0.39	97.7	0.38	0.38	100.3
SEL 12	0.42	0.43	102.5	0.40	0.42	105.3
H_2O 1	0.16	0.15	93.4	0.12	0.11	95.5
H_2O 2	1.17	1.16	98.8	1.25	1.25	99.9
H_2O 3	1.40	1.39	99.3	1.49	1.49	99.9
H_2O 4	2.60	2.58	99.0	2.76	2.74	99.5
H_2O 5	4.98	4.96	99.6	5.07	5.07	100.0
H_2O 6	6.18	6.15	99.5	6.19	6.17	99.6
H_2O 7	7.25	7.20	99.4	7.15	7.12	99.6
H_2O 8	0.22	0.18	80.7	0.16	0.14	90.2
H_2O 9	1.20	1.09	90.9	1.24	1.18	95.6
H_2O 10	1.46	1.43	97.8	1.53	1.51	98.9
H_2O 11	2.67	2.67	99.9	2.78	2.79	100.4
H_2O 12	5.03	5.01	99.7	5.09	5.08	99.9
H_2O 13	6.20	6.17	99.4	6.17	6.15	99.6
H_2O 14	7.32	7.30	99.7	7.17	7.16	99.8

Table 5
NIR model results for selamectin using in-process production samples

Sample	Claim (mg/ml)	HPLC (mg/ml)	NIR (mg/ml)	LC (mg/ml)	NIR (mg/ml)
248836	60.0	60.1	61.8	100.2	103.0
249455	60.0	59.6	61.3	99.3	102.2
250096	60.0	59.9	60.8	99.8	101.4
241604	60.0	60.5	61.7	100.8	102.8
241730	60.0	60.2	61.2	100.3	102.1
238854	60.0	60.1	60.8	100.2	101.3
237736	120.0	120.5	120.8	100.4	100.7
248974	120.0	120.5	119.0	100.4	99.2
249370	120.0	119.9	121.8	99.9	101.5
249879	120.0	120.6	120.7	100.5	100.6
236518	120.0	121.0	122.2	100.8	101.8
239344	120.0	122.4	119.6	102.0	99.7
241667	120.0	120.9	120.9	100.8	100.8
239451	120.0	120.7	120.8	100.6	100.7

Table 6
Precision of NIR model results for selamectin using in-process production samples

Precision sample 249371	NIR (mg/ml)				
Day 1					
A	120.8			Day 1 and 7	
B	120.6	Average	120.5	Average	120.8
C	120.5	S.D.	0.1	S.D.	0.4
D	120.5	% R.S.D.	0.12	% R.S.D.	0.34
E	120.5				
F	120.3				
Day 7					
G	120.6	Average	121.2		
H	121.2	S.D.	0.4		
I	121.7	% R.S.D.	0.34		
J	121.4				
K	120.9				
L	120.7				

Table 7
NIR models results for moisture using in-process production samples

Sample	KF (%)	NIR-full model (%)	NIR-HOH model (%)
248836	0.0	0.05	−0.01
249455	0.0	0.05	−0.01
250096	0.0	0.06	−0.01
241604	0.0	0.05	0.00
241730	0.0	0.11	0.00
238854	0.0	0.06	0.00
236518	0.0	0.03	0.00
239344	0.0	0.04	0.00
241667	0.0	0.03	0.00
239451	0.0	0.02	0.00
249570	0.0	0.01	0.00
249074	0.1	0.07	0.00
250864	0.0	0.02	0.00
249879	0.0	0.02	0.00

Table 8
Precision of NIR Models Results for Moisture using in-process production samples.

Precision sample 249371	NIR-full Model (%)	NIR-HOH model (%)
Day 1		
A	0.07	−0.02
B	0.08	−0.02
C	0.08	−0.01
D	0.09	−0.01
E	0.09	−0.01
F	0.09	−0.01
Day 7		
G	0.06	0.00
H	0.06	0.00
I	0.07	0.00
J	0.07	0.00
K	0.07	0.00
L	0.07	0.00

3.2.5. *Moisture analysis/NIR qualification*

The forty additional laboratory blends were again used to determine the accuracy of the NIR method for moisture as well (Table 3). The lab blends ranged from 0.5 to approximately 7.0% water in the topical formulation. The data confirms the NIR is providing equivalent accuracy for moisture as compared with Karl Fischer determinations for water content. In Table 3, the spectra data was analyzed with both the full NIR model and the second model solely for moisture determination. The simple regression applied to the full model NIR and titration results yields a correlation of 0.811, a slope of 1.03 and an intercept of −0.06. At 95% confidence, the t-test for the slope,

the F-test for the slope and the confidence interval for the slope all conclude that a significant relationship exists between the full model NIR results and Karl Fischer for moisture (Fig. 8). The simple regression applied to the H_2O model NIR and titration (Fig. 9) results yields a correlation of 0.963, a slope of 1.12 and an intercept of −0.124. At 95% confidence, the t-test for the slope, the F-test for the slope and the confidence interval for the slope illustrates that a significant relationship exists between the H_2O model NIR results and Karl Fischer for moisture.

A portion of the library 50–120% of a 60 mg/ml selamectin topical formulation was retested to illustrate precision for moisture determinations. (Table 4) The simple regression applied to the full model NIR results yields a correlation of 1.000, a slope of 0.996 and an intercept of −0.008. The simple regression applied to the H_2O model NIR results yields a correlation of 1.000, a slope of 0.997 and an intercept of 0.003. At 95% confidence, the t-test for the slope, the F-test for the slope as well as the confidence interval for the slope also concludes that a significant relationship exists between day 1 and day 2 results of both NIR models and the Karl Fischer determination for moisture.

3.2.6. *Application of the NIR Library*

Fourteen topical formulation samples were pulled during production and tested by the NIR and liquid chromatographic (Table 5) and Karl Fischer (Table 6) methods. The data again confirms the NIR is providing equivalent accuracy for potency and moisture. The simple regression applied to the NIR and LC results yields a correlation of 1.000, a slope of 0.996 and an intercept of 1.42. At 95% confidence, the t-test for the slope, the F-test for the slope and the confidence interval for the slope all conclude that a significant relationship exists between [1] the NIR result and the LC result and [2] the NIR result and the sample claim. A representative process sample at the 120 mg/ml selamectin topical formulation was repeated on a seventh day to illustrate longer term precision. (Tables 7 and 8) These samples yield a 0.34% R.S.D. over this period illustrating a strong precision and instrument stability over this period.

As a comparison, the NIR models yielded precision and accuracies for selamectin and moisture that were not significantly different from the liquid chromatographic and titration techniques already in use. Furthermore, the NIR was much more efficient in terms of time and should readily perform as a process analytical technique in the future. Because of its greater accuracy, the HOH model is the first model of choice for moisture determinations. This does not present an issue since the NIR instrument can be configured to process both models simultaneously and report the selamectin and moisture results in a real time mode.

4. Conclusion

The NIR method presented here was been qualified and found acceptable for use with the quantitative analysis of selamectin and moisture in topical formulations. This method was found to yield assay results not significantly different from the liquid chromatographic and titration assays for selamectin and moisture, respectively. This NIR procedure is the basis for an efficient and effective in-process monitoring of production as well as a check on finished good samples. The method can replace the titration moisture determination for release but, due to the lack of impurity or stability data, is not yet posed to replace liquid chromatographic release and stability testing at this time.

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