Spectrophotometric Determination of Pyrantel in Pyrantel Pamoate Bulk Samples and Pharmaceutical Formulations

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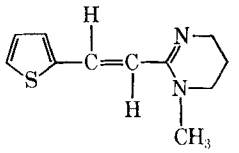
Abstract □ A spectrophotometric method for the determination of the pyrantel content of pyrantel pamoate bulk, oral suspension, and chewable tablets is described. This method involves the following sequence of steps: (*a*) dissolution of the sample in ammoniacal 1,4-dioxane solution; (*b*) removal of pamoic acid by precipitation with perchloric acid; (*c*) isolation of the pyrantel content by a two-stage extraction procedure; and (*d*) measurement of the pyrantel content of the final extract by UV absorption spectrophotometry. This analytical procedure for pyrantel circumvents any interference from pamoic acid and the potential degradation products [*i.e.*, (*E*)-*N*-(3-methylaminopropyl)-2-thiopheneacrylamide and the *cis*-isomer of pyrantel] of this anthelmintic agent.

Keyphrases □ Pyrantel pamoate, bulk, dosage forms—analysis □ Degradation products presence—pyrantel determination □ UV spectrophotometry—analysis

Pyrantel pamoate is an effective anthelmintic agent for human use (1–3). The chemical name of this drug is 1,4,5,6-tetrahydro-1-methyl-2-[*trans*-2-(2-thienyl)vinyl]-pyrimidine pamoate (1:1). A highly specific UV absorption spectrophotometric assay method has been developed for the determination of the pyrantel content of pyrantel pamoate bulk, oral suspension, and chewable tablets.

Pyrantel (I) exhibits UV absorption maximum at 311 nm. in aqueous 0.02 *N* hydrochloric acid. Pamoic acid, as well as two potential contaminants of pyrantel [the *cis*-isomer of pyrantel and (*E*)-*N*-(3-methylaminopropyl)-2-thiopheneacrylamide (II)], also exhibits absorption at this wavelength. These potential contaminants may be generated from pyrantel by photodecomposition and alkaline degradation, respectively. The UV absorption spectra of pyrantel, its *cis*-isomer, and (*E*)-*N*-(3-methylaminopropyl)-2-thiopheneacrylamide are illustrated in Fig. 1. The UV absorption spectrum of the *cis*-isomer of pyrantel is sufficiently different from that of pyrantel to permit the measurement of pyrantel in the presence of its *cis*-isomer by utilizing a two-component spectrophotometric technique (4, 5). Both (*E*)-*N*-(3-methylaminopropyl)-2-thiopheneacrylamide and pamoic acid would represent significant interferences in the spectrophotometric measurement of pyrantel unless previously removed.



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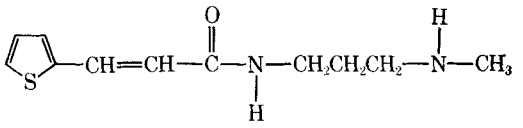

II

The assay procedure involves the following sequence of steps: (*a*) the sample is dissolved in aqueous ammonium hydroxide–1,4-dioxane (1:1, v/v); (*b*) pamoic acid is removed from this solution by precipitation with 0.5 *N* perchloric acid; (*c*) the cationic form of pyrantel is separated from the cationic form of the (*E*)-*N*-(3-methylaminopropyl)-2-thiopheneacrylamide by extraction into chloroform of the ion pair formed between the pyrantel cation and the perchlorate anion; (*d*) pyrantel is back-extracted into aqueous 0.02 *N* hydrochloric acid; and (*e*) the pyrantel content of this aqueous solution is determined by UV absorption spectrophotometry.

EXPERIMENTAL

Apparatus—A Varian Aerograph ultrasonic cleaner was utilized to facilitate the dissolution of pyrantel pamoate. A Cary spectrophotometer (model 11, 14, or 15) was used for recording the UV absorption spectra.

Reagents—Ammonium hydroxide, 1,4-dioxane, perchloric acid, hydrochloric acid, and chloroform were used.[1] In addition, reference samples of pyrantel tartrate, pyrantel pamoate, pamoic acid, the *cis*-isomer of pyrantel pamoate, the *cis*-isomer of pyrantel tartrate, and (*E*)-*N*-(3-methylaminopropyl)-2-thiopheneacrylamide hydrochloride were prepared in this laboratory.

Treatment of Sample—*Bulk Samples*—Approximately 100 mg. of sample was accurately weighed into a 200-ml. volumetric flask. This sample was dissolved in 10 ml. of 1,4-dioxane plus 10 ml. of 0.05 *N* ammonium hydroxide by placing the flask and its contents in the ultrasonic cleaner for approximately 5 min. This solution was then diluted to 200 ml. with 0.5 *N* perchloric acid, whereupon pamoic acid was precipitated. This suspension was clarified by the filtration procedure described later.

Oral Suspension—Approximately 1 ml. of the oral suspension was accurately weighed into a 20-ml. beaker. This sample was quantitatively transferred into a 250-ml. volumetric flask using 10 ml. of 1,4-dioxane and 10 ml. of 0.05 *N* ammonium hydroxide. The sample was completely dissolved by placing the flask and its contents into the ultrasonic cleaner for approximately 5 min. This solution was then diluted to 250 ml. with 0.5 *N* perchloric acid. The precipitated pamoic acid was removed by the filtration procedure described later.

Chewable Tablets—Each pyrantel pamoate tablet was reduced to a homogeneous powder using a mortar and pestle. The resulting powder was transferred to a 100-ml. volumetric flask using 0.05 *N* ammonium hydroxide–1,4-dioxane (1:1, v/v) as the wash solvent. The content of the flask was diluted to volume with this same solvent. Pyrantel pamoate was dissolved by placing the flask and its content in the ultrasonic cleaner for 10 min. The content of the flask was swirled several times during this period to ensure complete dissolution of the pyrantel pamoate. Only a white, insoluble precipitate remained after this treatment. A 15-ml. aliquot of the medium was diluted to 200 ml. with 0.5 *N* perchloric acid. The resulting suspension was clarified by filtration as described.

Filtration and Extraction—The suspension obtained from the previously described step was filtered through Whatman No. 2 filter paper. A 5-ml. aliquot of the clear filtrate was diluted to 50

[1] "Baker Analyzed" reagents, J. T. Baker, Phillipsburg, N. J.

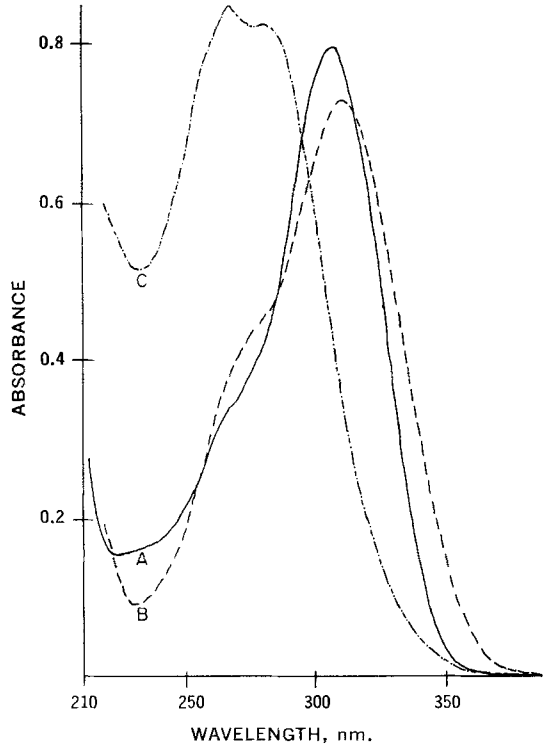

Figure 1—*UV absorption spectra in 0.02* N *hydrochloric acid. Key: A,* (E)-N-(*3-methylaminopropyl*)-*2-thiopheneacrylamide* (*4.3 mcg./ml.*), ——; *B, pyrantel* (*4.0 mcg./ml.*), - - -; *and C,* cis*-isomer of pyrantel* (*8.7 mcg./ml.*), —·—.

ml. with 0.5 *N* perchloric acid. A 25-ml. aliquot of this solution was transferred to a 250-ml. separator and extracted with two 100-ml. portions of chloroform. The chloroform phases were combined in a second separator and back-extracted with two 40-ml. portions of aqueous 0.02 *N* hydrochloric acid. The aqueous 0.02 *N* hydrochloric acid phases were combined in a 100-ml. volumetric flask. The separator was rinsed several times using 0.02 *N* hydrochloric acid as the wash solvent. These rinses were added to the volumetric flask and diluted to the mark with 0.02 *N* hydrochloric acid. The UV absorption spectrum of this solution was recorded *versus* 0.02 *N* hydrochloric acid as the reference solvent.

Determination of Fractional Recovery of Pyrantel—*Bulk Samples*—Synthetic mixtures of the reference samples of pyrantel tartrate and pamoic acid were taken through the assay procedure. The ratio of the pyrantel (milligrams) found (calculated from a Beer's law relationship) to pyrantel (milligrams) added represents the fractional recovery (RF^B) of pyrantel in the bulk assay procedure.

Oral Suspension and Chewable Tablets—The reference sample of pyrantel pamoate was taken through the assay procedure for the determination of pyrantel in oral suspension and chewable tablets. The ratio of the pyrantel (milligrams) found (calculated from a Beer's law relationship) to pyrantel (milligrams) added represents the fractional recovery (RF^{OS} or RF^{CT}) of pyrantel in the assay procedure for pyrantel in the oral suspension or chewable tablet formulations.

Calculation of Results—The pyrantel content of the final aqueous solution was determined using a two-component spectrophotometric technique (4, 5). This technique involves the measurement of the absorbances of a binary mixture of pyrantel and its *cis*-isomer at the isoabsorptive wavelength (267 nm.) and at the wavelength (311 nm.) of maximum absorbance of pyrantel. Using this technique, the pyrantel content of the final aqueous solution was calculated from the following equation:

$$C = \frac{[A^S_{311\text{ nm.}} \times a_{(267\text{ nm.})} - a^{(C)}_{(311\text{ nm.})} \times A^S_{267\text{ nm.}}]}{[a^{(T)}_{(311\text{ nm.})} - a^{(C)}_{(311\text{ nm.})}] \times L \times a_{(267\text{ nm.})}} \quad \text{(Eq. 1)}$$

where C is the pyrantel concentration in grams per liter; $A^S_{311\text{ nm.}}$ is the absorbance of the solution at 311 nm.; $A^S_{267\text{ nm.}}$ is the absorbance of the solution at 267 nm.; $a^{(C)}_{(311\text{ nm.})}$ is the absorptivity of the *cis*-isomer of pyrantel at 311 nm.; $a^{(T)}_{(311\text{ nm.})}$ is the absorptivity of pyrantel at 311 nm.; $a_{(267\text{ nm.})}$ is the absorptivity of pyrantel and its *cis*-isomer at the isoabsorptive point (267 nm.); and L is the cell path in centimeters.

The pyrantel content of bulk samples of pyrantel pamoate was then calculated from the following equation:

$$\%\text{ pyrantel} = \frac{C \times 8 \times 10^5}{\text{wt. (mg.) of sample} \times RF^B} \quad \text{(Eq. 2)}$$

In a similar manner, the pyrantel content of the oral suspension was calculated as follows:

$$\text{mg. pyrantel per ml. oral suspension} = \frac{C \times 10^4 \times \text{density}}{\text{wt. (g.) of sample} \times RF^{OS}} \quad \text{(Eq. 3)}$$

where the density of the oral suspension was expressed as grams per milliliter.

Finally, the weight of pyrantel per chewable tablet was calculated using the following equation:

$$\text{wt. (mg.) of pyrantel per chewable tablet} = \frac{C \times 5.33 \times 10^4}{RF^{CT}} \quad \text{(Eq. 4)}$$

Table I—Evaluation of Blanks in Oral Suspension Assay Procedure

No. of Determinations	[*A*(Blank)/*A*(Sample)] × 100 311 nm.	267 nm.
14	0.2 ± 0.1%[a]	1.9 ± 0.4%[a]

[a] Average ± *SD*.

Table II—Fractional Recovery of Pyrantel from Bulk and Pharmaceutical Formulations

No. of Determinations	Assay Procedure	Fractional Recovery (Average ± *SD*)
19	Bulk samples	$RF^B = 0.963 \pm 0.009$
19	Oral suspensions	$RF^{OS} = 0.967 \pm 0.008$
10	Chewable tablets	$RF^{CT} = 0.974 \pm 0.009$

RESULTS AND DISCUSSION

The blanks associated with the inactive ingredients of the chewable tablets and the oral suspension were evaluated. There was no significant blank associated with the chewable tablet assay proce-

Table III—Pyrantel Content of Pyrantel Pamoate Bulk Samples

Sample	Percent Pyrantel Found[a] (Average ± *SD*)	No. of Determinations
1	34.5 ± 0.1[b]	6
2	33.8 ± 0.3	3
3	34.5 ± 0.3	3
4	34.5 ± 0.1	4
5	34.6 ± 0.3	15
6	34.5 ± 0.3	3
7	34.4 ± 0.3	3
8	34.7 ± 0.2	3
9	34.3 ± 0.3	3
10	34.5 ± 0.3	3
11	33.7 ± 0.1	3
12	34.5 ± 0.2	6
13	34.7 ± 0.3	6
14	34.5 ± 0.2	6
15	34.5 ± 0.3	3
16	34.4 ± 0.2	4
17	34.6 ± 0.1	3
18	34.5 ± 0.1	3
19	35.0 ± 0.2	3

[a] Theoretical pyrantel content = 34.7%. [b] Average *SD* = ±0.2%.

Table IV—Pyrantel Content of Pyrantel Pamoate Oral Suspension Lots

Sample	Pyrantel Content[a] Found, mg./ml. (Average ± *SD*)	No. of Determinations
1	53.2 ± 0.4[b]	20
2	53.2 ± 0.5	5
3	53.7 ± 0.8	5
4	52.3 ± 0.7	6
5	51.2 ± 0.3	3
6	53.3 ± 0.3	6
7	53.1 ± 0.6	10
8	49.9 ± 0.6	3
9	51.7 ± 0.1	3
10	51.7 ± 0.2	3
11	52.5 ± 0.3	3

[a] Intended pyrantel content = 51.0 mg./ml. [b] Average *SD* = ±0.4 mg./ml.

Table V—Pyrantel Content of Pyrantel Pamoate Chewable Tablet Lots

Sample	Pyrantel Content[a] Found, mg./Tablet (Average ± *SD*)	No. of Determinations
1	264 ± 4.9[b]	10
2	268 ± 5.8	10
3	253 ± 4.8	10
4	260 ± 2.1	10
5	256 ± 2.7	10
6	260 ± 3.2	10
7	249 ± 3.6	10
8	254 ± 5.2	10

[a] Intended pyrantel content = 255 mg./tablet. [b] Average *SD* = ±4.0 mg./tablet.

dure. The blanks associated with the oral suspension procedure were both low and reproducible. A summary of the blank values for the oral suspension procedure is shown in Table I.

The fractional recovery values for pyrantel in the pyrantel pamoate bulk, oral suspension, and chewable tablet assays were both high and reproducible. Results of experiments designed to evaluate the fractional recovery values are listed in Table II. These data also indicate that the inert components of the oral suspension and the chewable tablets exert no significant effect on the fractional recovery of pyrantel in the assay procedure.

The fractional recovery values for the *cis*-isomer of pyrantel in the pyrantel pamoate bulk, oral suspension, and chewable tablet assays were evaluated by taking synthetic mixtures through the assay procedures. The fractional recovery values for the *cis*-isomer of pyrantel in the bulk, oral suspension, and chewable tablet assays were 0.91 ± 0.01, 0.90 ± 0.01, and 0.91 ± 0.01, respectively. These values indicate that approximately 90% of any *cis*-isomer present in the sample to be assayed would be carried through the assay procedure along with the pyrantel. The pyrantel content was calculated using a two-component spectrophotometric technique which served to correct for the presence of the *cis*-isomer of pyrantel.

The fractional recovery values for (*E*)-*N*-(3-methylaminopropyl)-2-thiopheneacrylamide were evaluated in the bulk, oral suspension, and chewable tablet assays. These fractional recovery values were 0.09 ± 0.01, 0.09 ± 0.01, and 0.07 ± 0.01, respectively. Consequently, greater than 90% of any (*E*)-*N*-(3-methylaminopropyl)-2-thiopheneacrylamide present in pyrantel pamoate bulk, oral suspension, and chewable tablets is removed from the pyrantel by the extraction procedure.

The separation of the pyrantel from the (*E*)-*N*-(3-methylaminopropyl)-2-thiopheneacrylamide was based on the fact that the cationic form of pyrantel and the perchlorate anion are capable of forming an ion pair which is extracted from an aqueous solution into chloroform (5–8). Under the conditions described in this assay, the (*E*)-*N*-(3-methylaminopropyl)-2-thiopheneacrylamide was only partially extracted (<10%) into the chloroform. Consequently, the ion-pair extraction served as a convenient method of eliminating the interference due to the presence of the (*E*)-*N*-(3-methylaminopropyl)-2-thiopheneacrylamide in the sample.

The interference due to the presence of the *cis*-isomer of pyrantel in the assay procedures for bulk, oral suspension, and chewable tablets was evaluated by taking synthetic mixtures of the pyrantel pamoate, its *cis*-isomer, and the inactive ingredients of the formulation through the assays. When these synthetic mixtures were taken through the bulk, oral suspension, and chewable tablet assay procedures, the percent of pyrantel found was 99.8 ± 0.9, 100.2 ± 0.9, and 100.9 ± 1.0, respectively. The data indicate that the presence of the *cis*-isomer of pyrantel does not interfere in the assay for pyrantel in pyrantel pamoate bulk, oral suspension, and chewable tablets.

The potential interference due to (*E*)-*N*-(3-methylaminopropyl)-2-thiopheneacrylamide was evaluated in an analogous manner. When synthetic mixtures of pyrantel pamoate and (*E*)-*N*-(3-methylaminopropyl)-2-thiopheneacrylamide were taken through the bulk, oral suspension, and chewable tablet assay procedures, the percent of pyrantel found was 100.2 ± 1.0, 100.9 ± 0.7, and 101.6 ± 1.4, respectively. These data indicate that contamination of pyrantel pamoate with up to 12% of this potential degradation product causes no significant interference in the assay procedures.

The assay procedure for pyrantel in pyrantel pamoate bulk samples was applied to 19 samples. The pyrantel contents found for these samples are listed in Table III. The percent pyrantel found for these 19 samples ranged from 33.7 to 35.0%. The theoretical content of pyrantel in pyrantel pamoate is 34.7%.

In addition, the assay for pyrantel in pyrantel pamoate oral suspension was applied to 11 formulated lots of the oral suspension. The average concentration found for these 11 lots ranged from 49.9 to 53.7 mg. of pyrantel per milliliter of oral suspension. The intended concentration of pyrantel in these formulated lots was 51 mg. of pyrantel per milliliter of oral suspension. These results are listed in Table IV.

Finally, the assay for pyrantel in pyrantel pamoate chewable tablets was applied to eight formulated lots of the chewable tablets. The pyrantel content found for these eight lots ranged from 249 to 268 mg. of pyrantel/tablet. The intended pyrantel content of these tablets was 255 mg./tablet. These results are reported in Table V.

SUMMARY

The recovery, blanks, reproducibility, and specificity of the assay procedure for the determination of the pyrantel content of pyrantel pamoate bulk samples and dosage forms were evaluated. This assay was applicable to the determination of pyrantel in pyrantel pamoate bulk samples, oral suspension, and chewable tablets in the presence of its potential degradation products [the *cis*-isomer of pyrantel and (*E*)-*N*-(3-methylaminopropyl)-2-thiopheneacrylamide].

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