ACKNOWLEDGMENTS AND ADDRESSES

Received August 25, 1975, from *K.M.K. College of Pharmacy, Ulhasnagar-3, District Thana, India.*

Accepted for publication April 2, 1976.

Adapted in part from a paper submitted by P. R. Shah to the University of Bombay, Bombay, India, in partial fulfillment of the Bachelor of Pharmacy degree requirements.

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Rapid Near IR Spectrophotometric Determination of Meprobamate in Pharmaceutical Preparations

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Abstract □ A rapid near IR spectrophotometric method was developed for determining meprobamate in tablets, sustained-release capsules, suspensions, and injectables. The absorbance of a chloroform solution of the drug is obtained at about 1.96 μm for quantitation. Assay of nine commercial products from four different manufacturers gave results ranging from 97 to 104% of label claim. Coefficients of variation of 0.7 and 1.3% were obtained on the tablets and a sustained-release product, respectively.

Keyphrases □ Meprobamate—IR spectrophotometric analysis, commercial dosage forms □ IR spectrophotometry—analysis, meprobamate, commercial dosage forms □ Sedatives—meprobamate, IR spectrophotometric analysis, commercial dosage forms

Since the USP XVIII (1) titrimetric procedure for determining meprobamate in tablets is lengthy and somewhat cumbersome, a rapid and easy-to-handle method is needed. A significant step toward this goal was taken by Sherken (2), who spectrophotometrically scanned chloroform solutions of the drug from 3.00 to 2.80 μm and utilized the absorbance at 2.91 μm to obtain the meprobamate concentration. This wavelength is characteristic of the symmetric stretching band of the primary amine group of meprobamate. However, for this procedure to be applicable, it was of paramount importance that the chloroform be freed of the stabilizer, alcohol. Therefore, extraction of the chloroform with water, followed by column chromatography through two tandem columns of activated alumina, was necessary.

Since the commencement of this work, USP XIX (3) adopted a colorimetric method for the assay of meprobamate in tablets. This method is sensitive and fairly rapid. However, the pH of the reagents must be carefully controlled and the acidified phenol reagent must be added carefully to decompose completely any chlorinating solution retained on the neck of the volumetric flask.

Because of the difficulties with these methods, a more rapid and facile procedure was desired that would be applicable to tablets and other dosage forms. The described near IR method is more rapid and does not suffer from the critical requirements of the other methods. Purification of the chloroform solution is not required since the alcohol does not interfere with the absorbance at 1.958 μm used to quantitate meprobamate. This band is subject to fewer interferences than the one at 2.91 μm (4). That the primary amine combination band at 1.958 μm is significantly weaker than the one at 2.91 μm also does not present any detection problem. High sensitivity is not of concern, because the levels of meprobamate in pharmaceutical preparations are generally high.

Table I—Comparison of Results Obtained on Commercial Products[a]

Sample	Label Claim, mg	Near IR Found, mg	Near IR Label Claim, %	USP XIX Found, mg	USP XIX Label Claim, %
1 (Tablet)	400	408	102.0	388	97.0
2 (Tablet)	400	403	100.8	393	98.3
3 (Tablet[b])	400	402	100.5	402	100.5
4 (Tablet)	200	205	102.5	200	100.0
5 (Tablet)	400	415	103.8	404	101.0
6 (Injectable[c])	400	394	98.6	400	100.0
7 (Capsule[d])	200	200	100.0	200	100.0
8 (Capsule[e])	300	295	98.3	355	118.0
9 (Suspension)	200	194	97.0	—	—
Mean			100.4[f]		99.5[g]

[a] Values reported are the average of duplicate assays. [b] Film-coated tablet. [c] Intramuscular injectable. [d] Sustained-release capsule. [e] Sustained-release capsule containing 15 mg of dextroamphetamine sulfate. [f] Samples 1–9. [g] Samples 1–7.

EXPERIMENTAL

Apparatus—A recording spectrophotometer equipped with an IR source[1] and matching 5-cm silica cells were used.

Reagents—Chloroform (reagent grade) and a standard solution of meprobamate (NF XIV), 3.0–4.0 mg/ml in chloroform, were used.

Sample Preparation—*Tablets*—Determine the average tablet weight of not less than 20 tablets. Reduce the tablets to a fine powder and accurately weigh a portion, equivalent to 300–400 mg of meprobamate, into a 100-ml volumetric flask. Add about 70 ml of chloroform to the flask and shake for 15–20 min. Dilute to volume with chloroform and filter through paper[2], discarding the first 15–20 ml.

Sustained-Release Capsules—Determine the average net fill of not less than 20 capsules. Shake the contents to obtain a representative sample. Triturate an accurately weighed sample, equivalent to 300–400 mg of meprobamate; transfer it to a 100-ml volumetric flask with the aid of about 70 ml of chloroform and shake for 15–20 min. Dilute to volume with chloroform and filter as described for tablets.

Suspensions—Shake the sample for several minutes so that a representative sample aliquot can be removed. With a "to contain" pipet, transfer an aliquot equivalent to about 400 mg of meprobamate to a separator. Rinse the pipet thoroughly with distilled water into the separator and add water, if necessary, to obtain a volume of about 30 ml.

[1] Cary model 14.

[2] Whatman No. 1.

Table II—Results of Precision Study on Sample 5

Determination	Amount Found, mg	
	Near IR	USP XIX
1	415	395
2	415	396
3	413	408
4	413	404
5	416	399
6	422	401
7	416	403
8	410	405
9	415	412
10	415	414
Mean	415	404
SD	3.1	6.3
CV	0.7	1.5

Extract with three 30-ml portions of chloroform, collecting the chloroform extracts in a 100-ml volumetric flask after filtering through a small amount of anhydrous sodium sulfate. Then dilute to volume with chloroform and mix well. Accurately weigh about 400 mg of meprobamate standard material into a separator, suspend the material in about 30 ml of water, and similarly extract with chloroform.

Injectables—Combine the contents of several ampuls and transfer an aliquot, equivalent to about 400 mg of meprobamate, to a separator. Add about 25 ml of distilled water and extract with chloroform as described for suspensions. Prepare a placebo solution containing the same amount of polyethylene glycol 400 as is found in the commercial ampul preparation. In addition, accurately prepare a standard of about 400 mg of meprobamate dissolved in the placebo solution and then extract as described for suspensions.

Assay Procedure—*Tablets, Sustained-Release Capsules, and Suspensions*—Balance the instrument at 2.00 μm with chloroform in both cells and then scan to 1.93 μm to establish the baseline. Record the spectra of the prepared samples and standard solutions *versus* chloroform over the same range (Fig. 1). Draw a line connecting the points on the curve at 1.945 and 1.980 μm. Obtain the absorbance difference (ΔA) between the absorbance maximum at about 1.958 μm and at the same point on the line drawn.

Injectables—Balance the instrument at 2.00 μm with the extracted placebo in both cells and then scan to 1.93 μm to establish the baseline. Record the spectra of the standard and ampul extracts *versus* the placebo extract over the same range.

Calculations—Calculate the quantity of meprobamate using:

$$\frac{\Delta A \times f \times d \times c}{s} = \text{mg meprobamate/capsule or tablet} \quad \text{(Eq. 1)}$$

or:

$$\frac{\Delta A \times f \times d}{v} = \text{mg meprobamate/ml of suspension or injectable} \quad \text{(Eq. 2)}$$

where ΔA = absorbance difference at 1.958 μm, f = standard factor in milligrams of meprobamate per milliliter per ΔA, d = dilution volume, c = average capsule fill or tablet weight in grams, s = sample weight in grams, and v = sample aliquot in milliliters.

RESULTS AND DISCUSSION

A series of standard solutions ranging from 2.0 to 7.0 mg/ml was analyzed, and adherence to Beer's law was observed. Nine commercial samples of meprobamate products from four different manufacturers were assayed by the near IR method and the USP XIX method (Table I). The near IR method can be successfully applied to various dosage forms including a combination product. A precision study, based on 10 separate determinations of a tablet preparation, was performed using both the near IR method and the USP XIX method (Table II).

When a suspension was assayed by the USP XIX colorimetric method, very low and widely scattered results were obtained. Similarly, when the same suspension was assayed by the USP XVIII titrimetric method, low results were obtained. During the hydrolysis step in the latter procedure, the suspension darkened to such an extent that the detection of the colorimetric end-point of the subsequent titration became extremely difficult.

When an intramuscular injectable was first assayed by the near IR method used to assay suspensions, it was immediately apparent that the spectra were distorted. The gross distortion was due to the large amount of polyethylene glycol 400 in the formulation (400 mg of meprobamate/5 ml of a 65% solution of polyethylene glycol 400). This problem was circumvented by "blanking out" this interference as already described. However, since the amount of polyethylene glycol 400 might vary by as much as ±10% of the label declaration, an experiment was performed to determine the effect of such a variation on the assay. The meprobamate extracted from a 65% polyethylene glycol 400 solution, when assayed against extracted placebos containing 58 and 72% polyethylene glycol 400, yielded recoveries of 99.7 and 101.0%, respectively. Thus, the proposed method is unaffected by variable amounts of polyethylene glycol 400. The results of the near IR method compare favorably with those obtained by the USP XIX method (Table I).

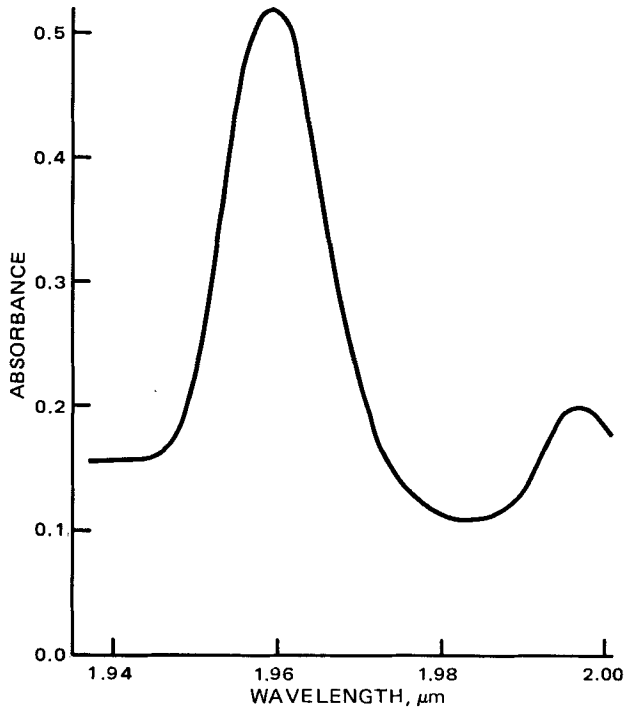

Figure 1—*Near IR absorption spectrum of meprobamate (4.17 mg/ml) in chloroform (5-cm cells).*

The product containing meprobamate in combination with dextroamphetamine gave a high result when assayed by the USP XIX procedure (Table I). This high value was partially due to dextroamphetamine reacting with the reagents. The dye used in the capsule also contributed to the high result. In contrast, dextroamphetamine and the dye did not cause any interference with the determination of meprobamate in this combination product by the near IR method.

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ACKNOWLEDGMENTS AND ADDRESSES

Received November 12, 1975, from the *Analytical and Physical Chemistry Laboratories, Planning and Operations, Pharmaceutical Research and Development, Smith Kline and French Laboratories Division, SmithKline Corporation, Philadelphia, PA 19101.*

Accepted for publication April 15, 1976.

Appreciation is expressed to Dr. Walter W. Holl for technical assistance.

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