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Opium Alkaloids XII: Quantitative Determination of Morphine in Opium by Isotope Dilution

EINAR BROCHMANN-HANSSEN

Abstract □ A method was developed for quantitative determination of morphine in opium based on the isotope dilution technique. Morphine-2-^{3}H and morphine-*N*-$^{14}CH_3$ are used as radioactive standards. A mixture of opium and the radioactive morphine standard is triturated with dimethyl sulfoxide, dispersed on diatomaceous earth and acidic aluminum oxide, and suspended in water. The aqueous suspension is transferred to a chromatographic column of acidic aluminum oxide, and the alkaloids are eluted with water. Alternatively, the mixture of opium and radioactive morphine is triturated with a little water and dispersed on diatomaceous earth, and the alkaloid bases are liberated with ammonia. The powder mixture is transferred to a column of neutral aluminum oxide and eluted with chloroform–isopropyl alcohol (3:1). Phenolic and nonphenolic alkaloids are separated by extraction at pH 13, and morphine crystallizes from the aqueous phase after adjustment of pH to 9. The crystals are collected and recrystallized to constant radioactivity. Both extraction methods gave the same results. No loss of tritium occurred during the assay, and morphine-2-^{3}H and morphine-*N*-$^{14}CH_3$ were equally satisfactory as radioactive standards. The method is specific for morphine, has good precision (0.4%), and requires no elaborate technique.

Keyphrases □ Opium alkaloids—analysis of morphine in opium by isotope dilution □ Morphine, in opium—analysis, isotope dilution method □ Isotope dilution method—analysis, morphine in opium

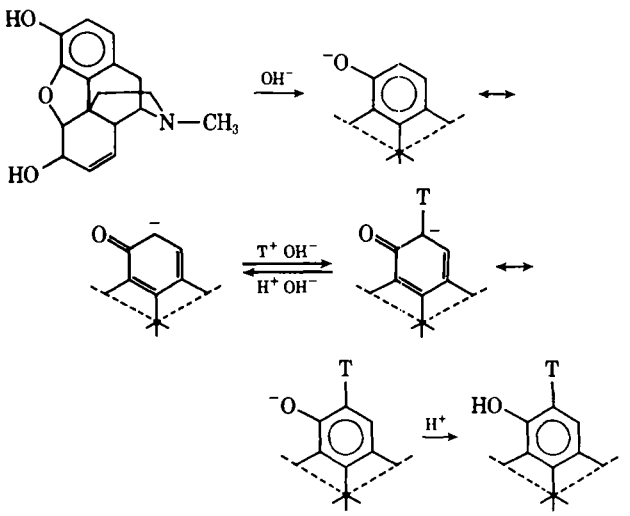
The lime method for assay of opium has remained relatively unchanged through several revisions of the USP (1). Nevertheless, it is well recognized that this method leaves much to be desired and does not give an accurate estimate of the morphine content of opium (2–4). In recent years, many attempts have been made to overcome the problems associated with the lime method and to develop assay procedures with better precision and accuracy.

DISCUSSION

Many modern pharmacopeias have adopted modifications of the method proposed by Mannich (5) in 1935, in which an aqueous solution of morphine is reacted with 1-chloro-(or fluoro)-2,4-dinitrobenzene in the presence of base. The slightly soluble dinitrophenyl ether of morphine crystallizes and can be determined gravimetrically or volumetrically. The extraction of morphine from opium is usually achieved with water or alcohol, and a partial purification is obtained by means of a chromatographic column of aluminum oxide. The many modifications of this technique were reviewed by Schultz and Schneckenburger (6). Loss of morphine may result from a slight solubility of the dinitrophenyl ether (3, 6). At the same time, the crystalline precipitate is often contaminated with minor opium alkaloids, with aluminum hydroxide, and with excess reagent or the corresponding phenol or amine (2, 3, 6, 7).

Other methods proposed for the assay of opium make use of liquid–liquid extraction techniques (8–11), ion-exchange resins (12–14), partition or adsorption chromatography (15–18), paper chromatography (19–21), TLC (22), GC (23), UV and IR spectrophotometry (17, 18, 22, 24, 25), colorimetry (11–13, 19, 20, 26, 27), and polarography (11, 28, 29). Although some of these methods may be superior to the USP lime method, no assay procedure reported to date is specific for morphine.

It is extremely difficult to obtain a complete separation of morphine from the complex mixture of alkaloids and nonalkaloidal matter associated with it without losing morphine in the process. Therefore, specificity can probably be achieved only by using a selective method for the quantitative estimation. The isotope dilution technique is such a method of exceptional selectivity. The principle of this method is to add a known amount of radioactive morphine standard to a sample of opium and then to isolate morphine and purify it to constant radioactivity. The difference in specific activity of the isolated morphine as compared to that of the radioactive



Scheme I—Base-catalyzed tritium labeling of morphine

Table I—Influence of Certain Variables on the Isotope Dilution Assay of Morphine by the Neutral Alumina Method

Volume of Eluate, ml.	Content of Morphine in Opium, %[a]					
	Radioactive Standard Added before Extraction			Radioactive Standard Added after Extraction		
	Number of Recrystallizations			Number of Recrystallizations		
	1	2	3	1	2	3
50	11.56	11.54	11.49	11.49	11.44	11.46
75	11.61	11.49	—	11.64	11.51	—
100	11.42	11.47	11.45	11.46	11.54	11.48
125	11.43	11.53	11.48	11.43	11.50	11.46
150	11.36	11.42	11.44	11.52	11.49	11.47

[a] Results expressed in percent based on at least two determinations.

standard is proportional to the amount of morphine in the sample. This technique is particularly suitable for the determination of morphine because this alkaloid can be readily purified by crystallization. When a homogeneous mixture of radioactive and nonradioactive morphine has been obtained, any losses due to oxidation, purification, or spillage will not affect the result, provided the radioactive label is stable and its presence does not alter the physical or chemical properties of the molecule (isotope effect).

The simplest method for preparation of radioactive morphine of high specific activity and purity is by tritium exchange in position 2 (30, 31). Morphine dissolved in dimethylformamide is sufficiently ionized at the phenol group to permit exchange with tritiated water according to Scheme I. The tritiation is carried out in a sealed tube at about 100°. An equilibrium condition is reached which depends on the specific activity of the tritiated water. The exchange reaction is reversible, and the tritium label may be removed by prolonged heating with aqueous dimethylformamide or with an aqueous methanol solution of potassium carbonate or other weak bases (31). Treatment with a strong base, such as 1 *N* NaOH, has little effect on the tritium label even at high temperatures, because the concentration of hydrogen ions is negligible. The labeling is exclusively in the 2-position. This has been confirmed by deuterium exchange under similar conditions and NMR spectroscopy (30). When it is pure, morphine-2-^{3}H may be crystallized from aqueous methanol or extracted with dilute acid or alkali without loss of activity. Another potential standard[1] is morphine-*N*-$^{14}CH_3$, which may also be easily synthesized (32) or prepared biosynthetically (33, 34). It was decided to try both these compounds and to compare their suitability as radioactive standards in the isotope dilution procedure.

The extraction of opium has always been a major problem in the assay. Extraction can be facilitated by dissolving the opium sample in dimethyl sulfoxide (18) and dispersing the solution on diatomaceous earth. A partial purification of the alkaloids may be achieved by means of a chromatographic column of aluminum oxide (4, 6, 15, 35, 36).

The isotope dilution technique was adapted for both acidic and neutral aluminum oxide. When acidic aluminum oxide was used, the opium sample and radioactive morphine standard were mixed and triturated with dimethyl sulfoxide, dispersed on diatomaceous earth and acidic alumina, and suspended in water. The suspension was transferred to a column of acidic alumina, and the alkaloids were eluted with water. Practically all radioactivity was contained in the first 50 ml. of eluate; the next 0.5 ml. displayed a number of counts equal to or slightly above background. The eluate was made strongly basic with sodium hydroxide and the minor alkaloids were extracted, first with a mixture of chloroform–isopropyl alcohol (4:1) and then with ether. Adjustment of pH to 9.0 with ammonium chloride and vigorous shaking with ether promoted crystallization of morphine.

In the neutral alumina method, opium and radioactive morphine standard were mixed and triturated with water and diatomaceous earth to a uniform powder. Ammonia was added to liberate the alkaloid bases, the mixture was transferred to a chromatographic column containing neutral aluminum oxide, and the alkaloids were eluted with a mixture of chloroform–isopropyl alcohol (3:1). The elution appeared to be quantitative with as little as 50 ml. of organic solvent (Table I). For routine analyses, 100 ml. of solvent mixture was generally used because this gave an eluate that was lighter in color and showed less tendency to cause emulsion problems when shaken with alkali. Morphine was extracted from the organic eluate with 0.1 *N* NaOH solution. The alkaline extract was adjusted to pH 9.0 with ammonium chloride and shaken with ether to remove minor alkaloids and promote crystallization of morphine. The results were the same whether the radioactive morphine standard was added to the opium sample prior to extraction or to the eluate from the column (Table I). However, it was considered best to carry the radioactive morphine through the entire procedure to eliminate any potential errors caused by oxidation or irreversible adsorption of morphine.

With either method, the crystals of morphine were filtered, washed, and recrystallized from aqueous methanol to constant radioactivity. No opium sample required more than two recrystallizations. The crystals were dried *in vacuo* to remove the solvent of crystallization, and the radioactivity was measured in a liquid scintillation spectrometer. No quenching was observed with any of the samples, and the use of an internal standard can be eliminated for routine analyses. The specific activities of the morphine samples were sufficiently high to yield a large number of counts (>25,000) in a few minutes. This reduced the random error of counting and the possibility of errors induced by drift of the instrument.

RESULTS

Table II gives the results of analyses of two samples of opium USP and four authenticated samples[2]. For comparison, the results reported in the literature for the same samples analyzed by other procedures are also given. It would appear, as has been stated by others, that the values of the USP method are about 10–15% too low.

There was no significant difference in the results whether morphine-2-^{3}H or morphine-*N*-$^{14}CH_3$ was used as the radioactive standard. This indicated that the tritium label was stable under the experimental conditions. Furthermore, both extraction methods gave identical results. The acidic alumina method is very simple and gives an aqueous eluate with only a light, yellowish-brown color. However, it is somewhat more time consuming because the elution with water is very slow unless pressure is applied. Also, because of the larger volume of water from which morphine crystallizes, it is often difficult to obtain a sufficient amount of crystals if the morphine content in opium is low (<8%). For the maximum yield of morphine, pH must be adjusted carefully to the isoelectric point of morphine.

It is of crucial importance in the isotope dilution method that morphine from the opium sample and the radioactive standard form a homogeneous mixture. Since the radioactive standard is used in the form of a base while morphine is present in opium as a salt, attempts were made to increase the homogeneity of the mixture by: (*a*) addition of a small amount of acid to the dimethyl sulfoxide (1 drop of concentrated sulfuric acid in 5 ml. of dimethyl sulfoxide), or (*b*) use of concentrated acetic acid instead of dimethyl sulfoxide. Neither modification gave results which were different from those of the original procedure.

When known amounts of anhydrous morphine were added to opium samples prior to extraction, the recoveries were 99.5–100.5% based on the average assay values obtained without added morphine. Recoveries of 99.6–100.2% were obtained when anhydrous

[1] Available from Amersham/Searle Corp.

[2] From the collection of the United Nations Division of Narcotic Drugs.

Table II—Determination of Morphine in Opium (Percent)[a]

Opium Sample	Isotope Dilution Method: Neutral Alumina ^3H	Isotope Dilution Method: Neutral Alumina ^{14}C	Isotope Dilution Method: Acidic Alumina ^3H	Isotope Dilution Method: Acidic Alumina ^{14}C	Other Methods
USP powder	11.47	—	11.52	—	9.70[b]
USP granular	11.69	11.69	11.71	11.71	10.50[b], 11.4[c]
UN 2 A	13.37	13.43	13.33	—	14.0[c], 13.95[d], 13.5[e]
UN 15	16.24	16.22	16.23	16.26	16.5[c], 16.17[d]
UN 25 A	18.53	18.50	18.39	18.40	18.3[c], 17.85[d], 18.1[e]
UN 38 G	17.54	17.58	17.50	17.46	17.51[d], 17.0[e]

[a] Average values of two or more determinations. [b] USP XVIII method (1). [c] GC method (23). [d] TLC (22). [e] Modified Mannich's method (38).

morphine was carried through the procedures without opium present. Addition of codeine, thebaine, papaverine, narcotine, and narceine in amounts that would double the percentages of these alkaloids normally found in opium had no effect on the determination of morphine.

After two recrystallizations, no impurities could be detected in the morphine crystals by GLC, TLC, or high-pressure liquid chromatography.

The precision of the isotope dilution method—both extraction procedures—was calculated to be 0.4% (relative standard deviation).

EXPERIMENTAL

Materials—Acid-washed diatomaceous earth[3] and Woelm aluminum oxides[4] were used for dispersion and partial purification of opium. All solvents were reagent grade. The chromatographic tube was 25 cm. long. The lower part, about 12–13 cm. in length, had an internal diameter of 10 mm.; the upper part, which served as a solvent reservoir, had an internal diameter of 22 mm. The tube was equipped with a fritted-glass disk of coarse porosity for support of the column packing. The scintillator solution was prepared by dissolving 5.5 g. of 91% 2,5-diphenyloxazole-9% dimethyl 1,4-bis-2-(4-methyl-5-phenyloxazolyl)benzene[5] in enough scintillation grade toluene to make 1 l.

Equipment—The radioactive morphine standard for dilution and the samples for scintillation counting were dried in a drying pistol at about 0.025 mm. Hg at a temperature of about 80° (boiling benzene) and weighed[6]. The radioactivity was determined with a liquid scintillation spectrometer[7]. The efficiency, determined with internal standards of radioactive toluene, was about 92% for ^{14}C and about 46% for ^3H.

Preparation of Labeled Morphine—Anhydrous morphine base was labeled by base-catalyzed tritium exchange as described by Battersby *et al.* (31), and the product was diluted with nonradioactive morphine to a specific activity of about 100,000 counts/min./mg. After five crystallizations from aqueous methanol, the crystals were dried *in vacuo* and stored in a tightly closed vial in a desiccator over Aquasorb[8] and protected from light.

Morphine labeled with ^{14}C in the *N*-methyl group was isolated from opium poppies which had been fed (±)-reticuline-*N*-$^{14}CH_3$ (37). After purification and drying, the anhydrous base had a specific activity of about 30,000 counts/min./mg.

Assay Procedures—*Acidic Aluminum Oxide Method*—Acidic aluminum oxide (2 g.) was placed in distilled water, and air bubbles were removed by stirring with a glass rod. Very fine particles were removed by repeated suspension and decantation, and the remainder was transferred to a chromatographic tube and allowed to settle. Water was drained off until it was level with the top of the aluminum oxide layer. One gram of opium and 10–20 mg. of radioactive morphine, accurately weighed, were placed in a glass mortar with a spout, and the mixture was triturated with 2 ml. of dimethyl sulfoxide for about 5 min. Diatomaceous earth (2 g.) was added gradually, and the trituration continued until a uniform paste was obtained. Acidic aluminum oxide, Activity IV (3 g.), was added to the mixture with gentle stirring, followed by 10 ml. of water; the mixture was stirred occasionally for 10–15 min. and transferred to the chromatographic tube. The stopcock was opened, and the eluate was collected in a 150-ml. separator. The mortar and pestle were rinsed with 3 × 5 ml. of water, and each washing was transferred to the chromatographic tube as the liquid reached the top of the column packing. Finally, the elution of alkaloids from the column was continued with water until 50 ml. had been collected in the separator.

After addition of 2 ml. of 4 *N* NaOH, the solution was extracted twice with 40 ml. of a mixture of chloroform–isopropyl alcohol (4:1) and once with 40 ml. of ether. The aqueous solution was collected in a 125-ml. conical flask containing 2.0 g. of ammonium chloride. When the ammonium chloride had dissolved, 1 ml. of an ammonium chloride–ammonium hydroxide buffer solution of pH 9.0 and 30 ml. of ether were added; the flask was stoppered, shaken vigorously, and placed in the refrigerator for crystallization of morphine. The crystals were collected on a fritted-glass filter of medium porosity, washed with ice-cold water, and air-dried with suction for a few minutes. The suction was turned off, the crystals dissolved on the filter in about 2–3 ml. of warm methanol, and the solution was filtered. The filtrate was heated gently, if necessary, to redissolve the morphine which had crystallized; then 2–3 drops of water were added and the solution was set aside to crystallize. This recrystallization was repeated twice, and the pure crystalline morphine base was dried *in vacuo* at 80° for 2–3 hr.

Neutral Aluminum Oxide Method—A small pledget of cotton was placed on top of the fritted-glass disk of the chromatographic tube, and 12–15 ml. of a mixture of chloroform–isopropyl alcohol (3:1) was added. Neutral aluminum oxide, Activity IV (2 g.), was poured into the column and allowed to settle. One gram of opium and 10–20 mg. of radioactive morphine standard, accurately weighed, were placed in a glass mortar with a spout and triturated with 1 ml. of water. Diatomaceous earth (2 g.) was added in small portions, and the trituration was continued until a uniform powder mixture was obtained. Finally, 0.5 ml. of concentrated ammonia was mixed in quickly and the powder was transferred to the chromatographic tube. The mortar and pestle were wiped with cotton moistened with chloroform–isopropyl alcohol (3:1), and the cotton was placed on top of the column packing. The alkaloids were eluted with 100 ml. of the chloroform–isopropyl alcohol mixture; the eluate was collected in a 250-ml. separator and extracted, first with 10 ml. and then with 5 ml. of 0.1 *N* NaOH. After each extraction the organic phase was drained into a flask, and the aqueous extract was transferred to a 50-ml. glass-stoppered flask by means of a 22.8-cm. (9-in.) disposable Pasteur pipet. Twenty milliliters of ether, 500 mg. of ammonium chloride, and 1 ml. of an ammonium chloride–ammonium hydroxide buffer solution of pH 9.0 were added; the flask was stoppered and shaken vigorously for about 2 min. and placed in a refrigerator. After about 1 hr. the crystalline precipitate was collected and purified by recrystallization as already described.

For determination of radioactivity, 1–1.5-mg. samples of the isolated morphine and the labeled morphine standards were weighed accurately, placed in separate counting vials, and dissolved in 0.2 ml. of methanol. Ten milliliters of scintillator solution was added to each vial. A blank of methanol and scintillator solution was prepared for determination of background counts.

The percentage of morphine in opium was calculated as follows:

$$\left(\frac{A}{B} - 1\right)\frac{100C}{D} = \%\ \text{morphine} \qquad \text{(Eq. 1)}$$

[3] Celite 545, Johns Manville Corp.
[4] Distributed by Waters Associates.
[5] Permablend I, Packard Instrument Co., Inc.
[6] On a Cahn Gram Electrobalance.
[7] Packard Tri-Carb, model 3375.
[8] Mallinckrodt Chemical Works.

where:

A = specific activity of radioactive morphine standard (counts/min./mg.)
B = specific activity of isolated morphine
C = amount of radioactive morphine standard added to the opium sample (mg.)
D = amount of opium used for extraction (mg.)

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Migration of Potent Drugs in Wet Granulations

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Abstract □ Sodium warfarin tablets prepared by a wet granulation method were shown to be unsatisfactory as to content uniformity due to the migration of the drug substance during the drying period. By using a TLC method, additives were selected which inhibited the migration of the drug substance. The use of these additives with sodium warfarin gave satisfactory tablets as to content uniformity when a wet granulation method was employed.

Keyphrases □ Tablets, content uniformity—migration during drying of water-soluble drug in wet granulations, evaluation of additive inhibitors □ Content uniformity, tablets—migration during drying of water-soluble drug in wet granulations, evaluation of additive inhibitors □ Migration of drugs in wet granulations—evaluation of additive inhibitors □ Sodium warfarin tablets—additive inhibition of drug migration in wet granu'ations □ Wet granulations—inhibition of water-soluble drug migration, evaluation of additives □ TLC—evaluation of additives for inhibition of sodium warfarin migration in wet granulations

Compressed tablets are one of the most widely used dosage forms for the administration of orally effective therapeutic agents. Among the requirements for a satisfactory tablet, content uniformity is of prime importance (1–4). Uniformity of the drug substance is dependent on the uniform distribution of the active ingredient, or ingredients, throughout the tablet, as well as maintaining a constant tablet weight (5). Some compendia