It may also exert some additional healing effect due to its direct inhibitory effect against pepsin. Pepstatin, an antiulcer agent, has been shown to act through this direct inactivation of pepsin (26).

The results of the present studies strongly suggest a significant inhibition of gastric peptic activity by the surfactant at concentrations well below the dosages of dioctyl sodium sulfosuccinate presently used in laxative therapy. Such an inhibition of pepsin may explain the antiulcerogenic effect of dioctyl sodium sulfosuccinate already observed in rats (16). An additional antiulcer effect of this medicinal surfactant may be due to its potent ability to decrease the volume of secretions and the amount of acid secreted as indicated by Lish (16).

Although dioctyl sodium sulfosuccinate may provide an antiulcer action, a reduction in the digestive capacity of the gastric juice for dietary proteins and possibly certain drug interactions (15) must be considered when evaluating this agent for possible therapy of peptic ulcer patients.

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# GLC Determination of Aprindine: Quantitation and Stability Measurement


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**Abstract** □ A GLC method of analysis of a new antiarrhythmic agent, aprindine, is described. The raw material of the new drug substance, supplied as the hydrochloride salt, is dissolved in deionized water, and the base is liberated by a 10% aqueous solution of sodium carbonate. Aprindine is extracted with chloroform and mixed with the internal standard, 5α-cholestane. GLC is performed on a glass column packed with 3.8% W-98 on Chromosorb W-HP. Quantitation is achieved by computer calculation of the peak area ratios. GLC–mass spectral analysis indicates that the observed peak is that of aprindine, with a molecular ion at *m/e* 322. The retention times of aprindine and the internal standard are 2.0 and 5.8 min, respectively. All synthetic precursors show a shorter retention time than aprindine. This GLC method is applied to the quantitative determination of aprindine as raw material and in capsule and ampul formulations. The method is also used to measure the stability of aprindine to acid, base, dry heat, refluxing, and UV light and to pH variations.



**Keyphrases** □ Aprindine—GLC analysis in pharmaceutical formulations, effect of dry heat, refluxing, UV light, and varying pH on stability □ GLC—analysis, aprindine in pharmaceutical formulations □ Stability—aprindine in pharmaceutical formulations, effect of dry heat, refluxing, UV light, and varying pH □ Antiarrhythmic agents—aprindine, GLC analysis in pharmaceutical formulations, effect of dry heat, refluxing, UV light, and varying pH on stability


Aprindine (I), *N,N*-diethyl-*N'*-(2-indanyl)-*N'*-phenyl-1,3-propanediamine, is a new potent antiarrhythmic agent (1) which can be administered both orally and intravenously. The drug is presently being used in humans (1, 2) and has a long-lasting action when taken orally (1, 3).

**Table I—Relative Retention Times (RRT) of Compounds Related to Aprindine**

| Identity[a] | Chemical Name | RRT[b] |
|---|---|---|
| P | Indene | N.D. |
| P | 2-Indanone | N.D. |
| P | 2-Indanol | N.D. |
| P | 2-Indanol methanesulfonate | 0.07 |
| P | *N*-Phenyl-2-indanamine | 0.17 |
| Aprindine | *N,N*-Diethyl-*N'*-(2-indanyl)-*N'*-phenyl-1,3-propanediamine | 1.00 |
| PDP | *N,N*-Diethyl-*N'*-phenyl-1,3-propanediamine | 0.07 |
| PDP | *N*-Ethyl-*N'*-(2-indanyl)-*N'*-phenyl-1,3-propanediamine | 0.81 |
| PDP | *N*-2-Indanyl-*N*-phenyl-1,3-propanediamine | 0.66 |

[a] P = synthetic precursor, and PDP = possible degradation product. [b] Retention times were measured relative to aprindine (RRT = 1.00). N.D. = compound not detected at the conditions used.

TLC (4), GLC (1, 5, 6), and radioactive scintillation counting of tritium (1, 3, 4) or $^{14}C$-labeled aprindine (7) have been used to assay the drug in biological studies. Since all published GLC methods were used for biological experimentation, a wide range of accuracy up to 10% (1) was tolerated. The validation of the methods in regard to precision, accuracy, and specificity was not demonstrated. Furthermore, the methods were not designed to quantitate aprindine as a raw material or in pharmaceutical preparations.

This paper presents a precise analytical procedure for the quantitation of aprindine with no interference from precursors or degradation products. The method also measures the stability of the new drug substance and some pharmaceutical preparations containing it.

## EXPERIMENTAL

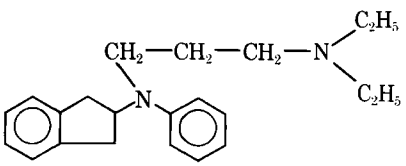
**Equipment**—A gas chromatograph[1] equipped with a flame-ionization detector was used. The detected signals were fed to a computer[2] for peak area integration and to a 1-mv recorder[3]. A U-shaped glass column (122 cm × 3 mm i.d.) was packed with 3.8% methyl vinyl silicone gum (W-98) on 80–100-mesh Chromosorb W-HP[4].

The following conditions were used: oven temperature, 230°; injection port temperature, 255°; detector temperature, 255°; helium carrier gas flow rate, 60 ml/min; hydrogen flow rate, 40 ml/min; and oxygen flow rate, 300 ml/min. Injections were made using a 10-$\mu$l syringe[5].

**Reagents and Chemicals**—The sodium carbonate[6] and chloroform[6] used were analytical reagent grade.

*Internal Standard Solution*—A solution of 60 mg of 5$\alpha$-cholestane[7]/50 ml of chloroform was used.

*Diluted Internal Standard Solution*—The internal standard solution was diluted 1 to 10 with chloroform.




aprindine

[1] Hewlett-Packard model 402, Avondale, Pa.
[2] Hewlett-Packard 2100.
[3] Honeywell Electronik-16, Honeywell, Philadelphia, Pa.
[4] Custom-made nontested packing, Ohio Valley Specialty Chemical, Inc., Marietta, Ohio.
[5] Hamilton No. 701, Reno, Nev.
[6] Mallinckrodt, St. Louis, Mo.
[7] Aldrich, Milwaukee, Wis.

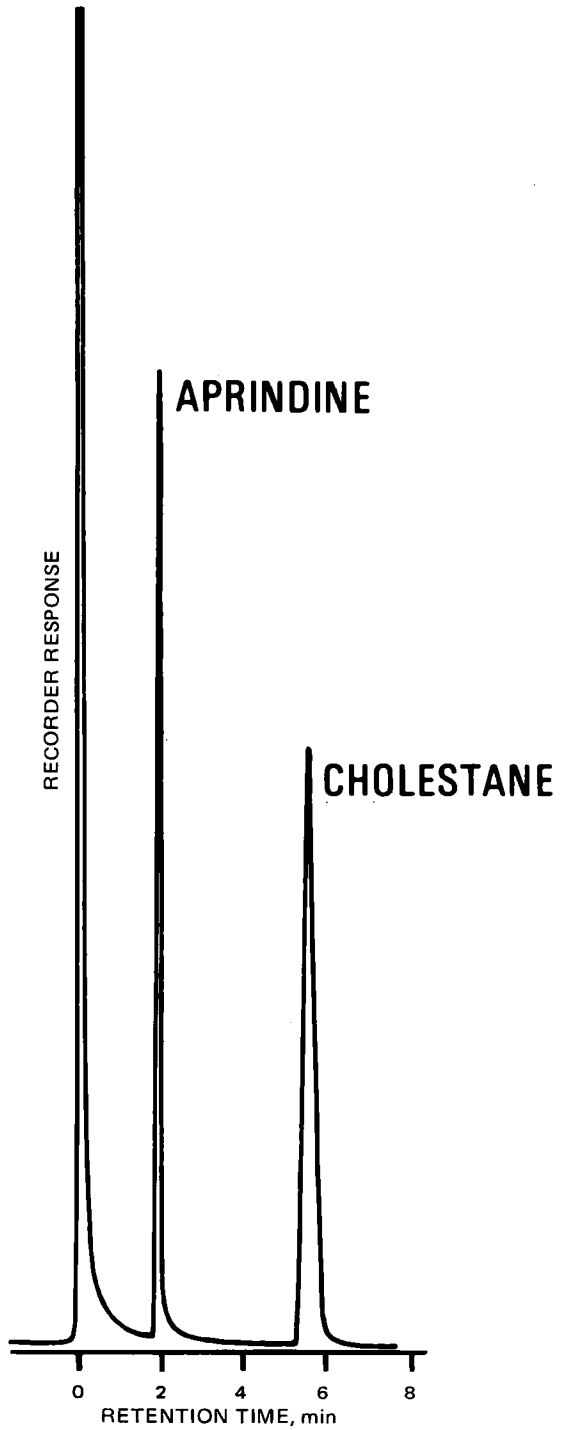



**Figure 1**—*Typical gas–liquid chromatogram of aprindine.*

**Preparation of Raw Material**—*Sample Solution*—Twenty-five milliliters of 10% sodium carbonate solution was added to 50 mg of the raw material dissolved in 5 ml of water in a separator, and the sample was extracted with three 10-ml portions of chloroform. The chloroform extracts were filtered through anhydrous sodium sulfate into a 50-ml volumetric flask. After dilution to volume with chloroform, the sample was mixed 1:1 with the internal standard solution.

*Standard Solution*—Fifty milligrams of reference standard aprindine hydrochloride was prepared in the same manner as the sample.

**Preparation of Capsule Formulations**—*Sample Solution*—The average fill weight of 10 capsules was determined. A portion of the capsule contents equivalent to 100 mg of aprindine hydrochloride was extracted from 15 ml of 10% sodium carbonate solution with three

Table II—Degradation Studies: Percent Recovery of Aprindine Determined by GLC

| Treatment | Hours | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | 2 | 6 | 12 | 24 | 48 | 72 | 144 |
| Reflux in 1 *N* methanolic hydrochloric acid | 100.6 | — | — | — | 100.4 | — | 99.5 | 99.0 |
| Reflux in 1 *N* methanolic potassium hydroxide | 102.0 | — | — | — | 102.5 | — | 101.1 | 101.5 |
| Reflux in methanol | 101.1 | — | 101.4 | 100.3 | 99.2 | — | — | — |
| Irradiation with UV light | 99.7 | 57.4 | 27.0 | 21.0 | 15.6 | 7.6 | — | — |
| Heat at 110° | 100.0 | — | 100.5 | 100.5 | 99.7 | — | — | — |
| Solution in 5% dextrose in water at 50° | 100.5 | — | 100.9 | 100.4 | 99.8 | — | — | — |
| pH Profile at 50° | | | | | | | | |
| pH 1.0 | 101.0 | — | 100.5 | 99.4 | 100.4 | — | — | — |
| pH 4.0 | 101.7 | — | 101.5 | 101.5 | 100.9 | — | — | — |
| pH 7.0 | 101.5 | — | 102.0 | 101.2 | 100.5 | — | — | — |

30-ml portions of chloroform. After dilution to 100 ml with chloroform, the sample was mixed 1:1 with the internal standard solution.

*Standard Solution*—One hundred milligrams of reference standard aprindine hydrochloride was extracted in the same manner as the capsule sample.

**Preparation of Lyophilized Ampul Formulations**—*Sample Solution*—The contents of one ampul (100 or 200 mg of aprindine hydrochloride) dissolved in 10 ml of water were extracted from 25 ml of 10% sodium carbonate solution with three 30-ml portions of chloroform. After dilution with chloroform to a concentration of 1 mg/ml, the sample solution was mixed 1:1 with the internal standard solution.

*Standard Solution*—One hundred milligrams of reference standard aprindine hydrochloride was extracted in the same manner as the ampul sample.

**Preparation of Solution Formulations (1 mg/ml)**—*Sample Solution*—A 5-ml aliquot was extracted from 20 ml of 10% sodium carbonate solution with three 10-ml portions of chloroform. After dilution to 50 ml with chloroform, the sample solution was mixed 1:1 with the diluted internal standard solution.

*Standard Solution*—A 1-mg/ml solution of reference standard aprindine hydrochloride in water was prepared. A 5-ml aliquot was extracted in the same manner as the solution formulation sample.

*GLC*—Two-microliter portions of the sample and standard solutions were injected, and the instrument parameters were adjusted to obtain the optimum response of the two peaks. The retention times were approximately 2.0 and 5.8 min for aprindine and cholestane, respectively.

*GLC–Mass Spectrometry*—A 70-ev electron-impact mass spectrum of the observed GLC aprindine peak was obtained using a gas chromatograph–mass spectrometer[8].

*Calculations*—For each chromatogram, the ratio ($R$) of the area of the aprindine peak to that of the internal standard was determined. The purity of the raw material is given by:

$$\text{milligrams of aprindine hydrochloride per gram} = \frac{R_{\text{sample}}}{R_{\text{standard}}} \times \frac{\text{milligrams of standard}}{\text{milligrams of sample}} \times \text{standard purity} \times 1000 \quad \text{(Eq. 1)}$$

The potency of the formulations is given by:

$$\text{milligrams of aprindine hydrochloride per capsule} = \frac{R_{\text{sample}}}{R_{\text{standard}}} \times \frac{\text{milligrams of standard}}{\text{grams of sample}} \times \text{average fill weight (grams)} \times \text{standard purity} \quad \text{(Eq. 2)}$$

$$\text{milligrams of aprindine hydrochloride per ampul} = \frac{R_{\text{sample}}}{R_{\text{standard}}} \times \frac{\text{milligrams of standard}}{\text{milliliters of standard solution}} \times \frac{\text{milliliters of sample solution}}{1 \text{ ampul}} \times \text{standard purity} \quad \text{(Eq. 3)}$$

[8] LKB 9000S, Produkter AB, Bromma, Sweden.

$$\text{milligrams of aprindine hydrochloride per milliliter of solution} = \frac{R_{\text{sample}}}{R_{\text{standard}}} \times \frac{\text{milligrams of standard}}{\text{milliliters of standard solution}} \times \text{standard purity} \quad \text{(Eq. 4)}$$

**Degradation Studies**—*Reflux in Acid, Base, and Methanol*—Solutions containing 1 mg of aprindine hydrochloride/ml in methanol, methanolic 1 *N* HCl, and methanolic 1 *N* KOH were prepared. Twenty-five-milliliter aliquots of each were refluxed for 24, 72, and 144 hr.

*UV Irradiation of Solution*—A solution containing 1 mg of aprindine hydrochloride/ml in water was prepared. Ten-milliliter aliquots were placed in quartz test tubes[9] and irradiated with UV light[10] for 2, 6, 12, 24, and 48 hr.

*Heat: Solid*—Twenty-five-milligram samples of aprindine hydrochloride were accurately weighed and placed in an oven at 110°. Samples were removed at 6, 12, and 24 hr.

*Heat: Solution*—Solutions containing 1 mg of aprindine hydrochloride/ml in 5% dextrose in water[11] and in buffers at pH 1, 4, and 7 were prepared. Twenty-five-milliliter aliquots were heated at 50° for 6, 12, and 24 hr.

All treated aqueous solutions were assayed by the addition of sodium carbonate solution and extraction into chloroform. The methanolic solutions were evaporated to dryness under vacuum and then extracted from sodium carbonate solution into chloroform. The oven-heated samples were dissolved in water, treated with sodium carbonate solution, and extracted into chloroform.

Appropriate aliquots (equivalent to 1 mg of aprindine hydrochloride) were evaporated to dryness with mild heat and an air stream and then redissolved in 1 ml of chloroform and 1 ml of internal standard solution. These solutions were assayed by GLC, using a standard solution prepared according to the raw material preparation.

## RESULTS AND DISCUSSION

Hydrochloride salts generally give chromatographic peaks of the same retention time as the base, but nonreproducible results and tailing peaks are frequently encountered. For this reason, aprindine base is chromatographed instead of the salt. A typical gas chromatogram is shown in Fig. 1. The first peak is aprindine, which was confirmed by GLC–mass spectrometry. The mass spectrum showed the expected molecular ion at $m/e$ 322. A linear response to aprindine raw material was obtained from 0.5 to 1.5 mg/ml.

To test the specificity of this GLC method for assaying aprindine, several related compounds, including its synthetic precursors, were chromatographed (Table I). All tested compounds had a retention time less than that of aprindine. To measure the retention times accurately, the column temperature was reduced to 200°. At this temperature, all compounds except indene, 2-indanone, and 2-indanol were detected. These three compounds were not resolved from the solvent front. Further lowering of the column temperature was not convenient for the assay due to the resulting increase in the retention

[9] 150 × 18 mm, MISCO Scientific, Berkeley, Calif.

[10] Hanovia lamp analytic model 7420, equipped with a high-pressure 325-w mercury vapor quartz lamp, Hanovia Lamp Division, Canrad Precision Industries, Newark, N.J. The tubes were about 15 cm from the lamp.

[11] D5W, Abbott Laboratories, North Chicago, Ill.

time of aprindine. None of the eight compounds tested interfered with the aprindine peak (Table I).

Duplicate injections of five 50-mg raw material samples, extracted by a single analyst, gave a standard deviation (*SD*) of 0.01 and a relative standard deviation [*RSD* = (*SD* × 100)/mean] of 1.48%. Duplicate injections of five capsule samples containing 25 mg/capsule gave a relative standard deviation of 1.04%. The relative error calculated for this formulation was +0.2%. Duplicate injections of five solution samples (1 mg/ml) gave a relative standard deviation of 0.79%.

No extra peaks were observed in the chromatograms of the refluxed or heated samples. Table II summarizes the results of the various degradation studies. With the exception of samples irradiated with UV light, the data indicate that aprindine is stable to these artificial degradation conditions. Analysis of the UV-irradiated solution showed detectable extra peaks. These were identified on the basis of their retention times to be *N*-phenyl-2-indanamine (II) and *N,N*-diethyl-*N'*-phenyl-1,3-propanediamine (III).

The formation of II and III may be due to a UV light-catalyzed homolytic cleavage of the appropriate carbon–nitrogen bond. Compounds II and III were reported previously as metabolites of aprindine (1, 4). None of the degraded solutions showed any interference with the assay of aprindine. Due to the light sensitivity of aprindine, ampul formulations must be protected from light. Natural shelflife stability data on raw material and capsule formulations for 2 years and on ampuls for 1 year indicate that the material is stable.

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# Comparative Plasma Concentrations of Quinidine following Administration of One Intramuscular and Three Oral Formulations to 13 Human Subjects


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**Abstract** □ Three oral dosage forms of quinidine sulfate (*i.e.*, tablet, capsule, and solution) and one intramuscular formulation of quinidine gluconate were administered to 13 healthy volunteers in a randomized complete crossover design. The plasma concentration of quinidine following each dose (equivalent to 167 mg of quinidine) was determined at 0.25, 0.50, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hr following dosing. Three conclusions were derived from analysis of the plasma concentration *versus* time data. First, the intersubject and intrasubject variability in the half-life of quinidine is large and should be considered in evaluating the bioavailability of quinidine. Second, the intramuscular quinidine gluconate gives a greater bioavailability than the quinidine sulfate tablet. And finally, the relative bioavailability of the quinidine sulfate capsule and solution administered orally as compared with the intramuscular quinidine gluconate depends on the methods employed to evaluate the plasma concentration *versus* time data.



**Keyphrases** □ Quinidine—pharmacokinetics and bioavailability of different dosage forms compared □ Pharmacokinetics—quinidine, different dosage forms compared □ Bioavailability—quinidine, different dosage forms compared □ Dosage forms—tablets, capsules, solutions, and intramuscular quinidine, pharmacokinetics and bioavailability compared □ Antiarrhythmic agents—quinidine, pharmacokinetics and bioavailability of different dosage forms compared


Quinidine is widely recognized as a clinically useful antiarrhythmic agent (1, 2). The plasma concentration *versus* time plots following both single and multiple doses were studied in several species of laboratory animals (3, 4) and in a relatively small number of humans (5–8). Intravenously administered quinidine hydrochloride gave varying plasma half-life values, depending on the species of laboratory animal (3).

Three different salts of quinidine (*i.e.*, sulfate, gluconate, and polygalacturonate) and dihydroquinidine gluconate were administered by mouth to 11 patients in both single- and multiple-dose studies (5). Following a single dose of quinidine sulfate, the maximum mean plasma concentration was 4.02 ± 0.74 (*SD*) μg/ml 2 hr after dosing. With multiple dosing, the gluconate and sulfate salts (in doses equivalent to 400 mg of quinidine sulfate every 8 hr) were most effective and gave steady-state plasma levels between 4 and 7 μg/ml.

The serum quinidine concentrations were determined in 17 patients taking 1–3 g of quinidine sulfate/day (6). The serum quinidine concentration following a single 664-mg dose of quinidine sulfate was measured at frequent intervals over 24 hr. The maximum serum concentration ranged from about 4 to 6 μg/ml, and the time to reach the maximum serum concentration ranged from 2 to 5 hr.

Three different oral quinidine preparations were administered to seven healthy volunteers in a comparative bioavailability study (7). The mean steady-state