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ACKNOWLEDGMENTS

Utility of Chloranil in Assay of Naphazoline, Clemizole, Penicillin G Sodium, and Piperazine

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Abstract □ A simple and sensitive spectrophotometric method is described for the assay of naphazoline, clemizole, penicillin G sodium, and piperazine. The method was based on the formation of a charge transfer complex between these drugs as n-donors and chloranil, the π-acceptor. Conformity to Beer's law enabled the assay of dosage forms of these drugs. Compared with official methods, the results obtained were of equal accuracy. A more detailed investigation of the naphazoline–chloranil complex was made with respect to its composition, association constant, and free energy change.

Keyphrases □ Naphazoline—spectrophotometric assay in dosage forms using complex formation with chloranil □ Clemizole—spectrophotometric assay in dosage forms using complex formation with chloranil □ Penicillin G sodium—spectrophotometric assay in dosage forms using complex formation with chloranil □ Piperazine—spectrophotometric assay in dosage forms using complex formation with chloranil

Naphazoline and clemizole (antihistamines), penicillin G sodium (antibiotic), and piperazine (anthelmintic) are widely used in pharmaceutical practice. The official compendia describe a nonaqueous titration for naphazoline (1), an iodometric titration (2) and microbiological assay (3) for penicillin G sodium, and a gravimetric method (1) and nonaqueous titration (3) for piperazine. Among the methods described for the assay of naphazoline are UV

spectrophotometry (4), colorimetry using reagents such as bromine (5), sodium nitroprusside (6), or ceric sulfate (7), and nonaqueous titration (1, 8).

Clemizole was determined spectrophotometrically applying Glenn's method of orthogonal function (9). Penicillin G sodium was assayed by different methods, including atomic absorption spectrophotometry (10), colorimetry through hydroxamic acid formation (11), IR spectrophotometry (12), polarography (13), and titrimetric methods involving iodine (2, 14), iodine monochloride (15), mercuric ion (16), and N-bromosuccinimide (17) as titrants. The proposed methods for the assay of piperazine include colorimetric analyses employing ammonium reineckate (18), bromthymol blue (19), sodium β-naphthoquinone-4-sulfonate (20), and 3,5-dichloro-p-benzoquinonechlorimine (21), and dichlone (22), titrimetry in nonaqueous solvents (3), and indirect complexometry (23).

Substituted quinones such as 2,5-dichloroquinone (24), 7,7',8,8'-tetracyanoquinodimethane (25), and fluoranil (26) were used as π-acceptors with various electron donors to form charge transfer complexes and radical ions (27, 28). Some aromatic amines (29, 30) and amino acids (31, 32) were determined with chloranil. The present report describes the utility of chloranil for the spectrophotometric determination of naphazoline, clemizole, penicillin G sodium, and piperazine in dosage forms. In addition, the naphazoline–chloranil complex with respect to its association constant, mole ratio of reactants, and free energy change ($\Delta G°$) was investigated.

EXPERIMENTAL

Instruments—A photoelectric spectrophotometer[1] with 1-cm silica or glass cells was used.

Materials and Reagents—Pharmaceutical grade naphazoline hydrochloride[2], clemizole hydrochloride[3], penicillin G sodium[3], and piperazine[4] were used as working standards.

p-Chloranil[5] was purified according to a literature method (33). The solution was prepared in chloroform (2×10^{-3} M) or dioxane (0.1 g %); the solvents were spectrograde.

Standard Solutions—For naphazoline and clemizole, the calculated amount (equivalent to 0.1 g of base) was dissolved in water. The solution was transferred quantitatively to a separator, alkalinized with ammonia, and extracted by shaking with five 20-ml portions of chloroform. The extracts were pooled in a 100-ml volumetric flask, and the flask was filled to volume with chloroform (1 ml contained 1 mg of the base).

For penicillin G sodium, 0.500 g of the drug was dissolved in 80% dioxane in water, and the solution was diluted quantitatively to give a concentration of 10 mg/ml.

For piperazine, 25.0 mg of the drug was placed in a 25-ml volumetric flask containing 5 ml of ethanol (95%), and the flask was shaken well before it was filled to volume with dioxane.

Determination of Naphazoline—For calibration, serial volumes of 1–5 ml (in 1-ml steps) of standard base solution, diluted four times to give 0.25 mg/ml, were transferred to 25-ml volumetric flasks. Sufficient chloroform was added to bring the volume to ~10 ml, and 5 ml of chloranil (2×10^{-3} M in chloroform) was added. The contents were mixed and heated in a water bath at 40 ± 1° for 24 min. The volume was brought to 25.0 ml with chloroform. The absorbance at 515 nm was measured against a blank, prepared simultaneously without naphazoline solution.

For the determination of naphazoline in eye drops, 10.0 ml (equivalent to 5.0 mg of naphazoline hydrochloride) was measured, the base was extracted as described previously with five 10-ml portions of chloroform,
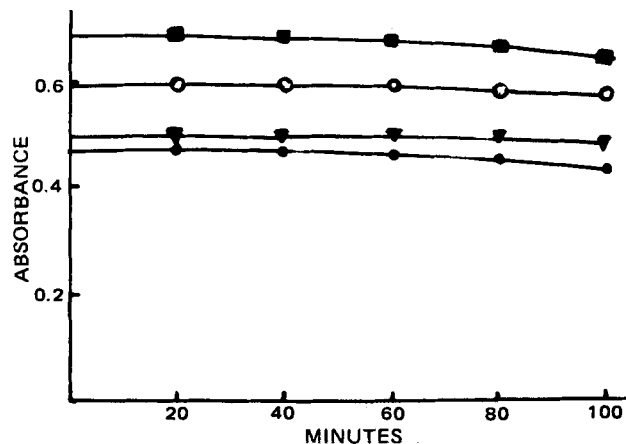

Figure 1—*Plot of absorbance versus time for complexed naphazoline (3 mg %) (○), clemizole (5 mg %) (●), penicillin G sodium (30 mg %) (▼), and piperazine (10 mg %) (■).*

and the extracts were pooled in a 50-ml volumetric flask. Using ~6 ml (accurately measured) of the base solution, the procedure given for calibration of naphazoline was followed.

Determination of Clemizole—For calibration, serial volumes of 2–9 ml (in 1-ml steps) of the standard solution were diluted quantitatively with chloroform to 25 ml. Exactly 1.0 ml of these diluted solutions, containing 0.08–0.36 mg, was measured into clean, dry test tubes. To each test tube were added 2.0 ml of chloranil solution (0.1 g % in dioxane) and 1.0 ml of dimethylformamide. The test tubes were maintained in a water bath at 25 ± 1° for 30 min. A blank was prepared simultaneously without clemizole solution. The absorbance was measured against the blank at 550 nm.

For the determination of clemizole in commercial tablets, 10 tablets were powdered and mixed. About 0.4 g (equivalent to two tablets) was transferred to a separator containing ~20 ml of water. The base was extracted as described with five 10-ml portions of chloroform, and the extract was diluted five times with chloroform. Exactly 1.0 ml of the diluted solution was measured, and the procedure for calibration of clemizole was followed.

Determination of Penicillin G Sodium—For calibration, serial volumes of 1–6 ml (in 1-ml steps) of the standard solution were transferred to 25-ml volumetric flasks and diluted quantitatively with 80% dioxane in water. Exactly 1.0 ml of the diluted solutions, containing 0.4–2.4 mg of penicillin G sodium, was measured into a series of clean, dry test tubes. To each test tube were added 2.0 ml of chloranil (0.1 g % in dioxane) and 1.0 ml of dimethylformamide. The test tubes were heated in a water bath at 40 ± 1° for 15 min. A blank was prepared simultaneously by substituting 1.0 ml of 80% dioxane in water for the penicillin G sodium solution. The absorbance was measured against the blank at 560 nm.

For the determination of penicillin G sodium in vials, the contents of one vial were dissolved in 80% dioxane in water. This solution was transferred quantitatively to a 25-ml volumetric flask and diluted 10 times with the same solvent. Using 1.0 ml of the diluted solution, the procedure for calibration of penicillin G sodium was followed.

Determination of Piperazine—For calibration, serial volumes of 1–5 ml of the standard solution (in 1-ml steps) were diluted in 10-ml volumetric flasks with dioxane. Exactly 1.0 ml of these solutions (equivalent to 0.1–0.5 mg) was pipetted into a series of clean, dry test tubes. Exactly 2.0 ml of chloranil (0.1 g % in dioxane) and 1.0 ml of dimethylformamide were added, and the solution was heated in a water bath at 60 ± 1° for 10 min. A blank was prepared simultaneously using 1.0 ml of dioxane instead of piperazine solution. The absorbance was measured at 540 nm against the blank.

For the determination of piperazine in powdered form, 25.0 mg of the powder was transferred to a 25-ml volumetric flask containing 5 ml of ethanol (95%). The flask was shaken well before it was filled to volume with dioxane. The solution was diluted four times with dioxane using 1.0 ml of the diluted solution, and the procedure for calibration of piperazine was followed.

Ratio of Reactants in Naphazoline–Chloranil Complex—Into 25-ml volumetric flasks was transferred 10 ml (varied in 1-ml steps) of an equimolar concentration (10^{-3} M) of solutions of naphazoline and chloranil in chloroform. The procedure was continued as described for the calibration of naphazoline.
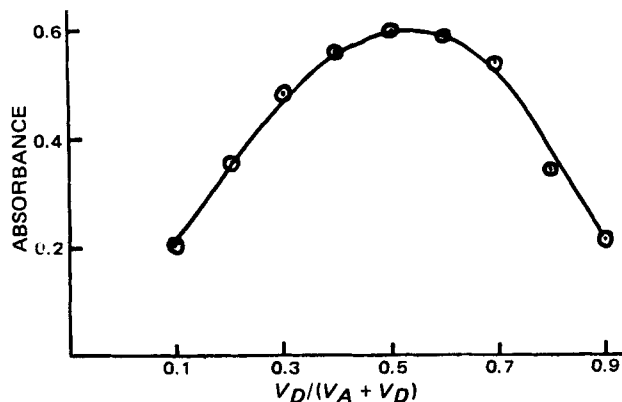
Figure 2—*Continuous variation plot for naphazoline–chloranil complex in chloroform (10^{-3} M).*

Determination of Association Constant and Free Energy Change—Serial volumes of 1–5 ml of 10^{-3} M naphazoline solution (in 1-ml steps) in chloroform were transferred to 25-ml volumetric flasks. The solution was diluted with chloroform to 10 ml, and 2.0 ml of chloranil solution in chloroform (2×10^{-3} M) was added. The procedure was continued as described for the calibration of naphazoline.

RESULTS AND DISCUSSION

In spite of their structural variation, naphazoline (I), clemizole (II), penicillin G sodium (III), and piperazine (IV) give a purple chromagen with chloranil that exhibits a strong absorption maximum at 515–560 nm, *i.e.*, in the visible region of the spectrum. These bands can be attributed to the formation of charge transfer complexes between I–IV, acting as n-donors (D) or Lewis bases, and chloranil, the π-acceptor (A) or Lewis acid (Scheme I).

$$\ddot{D} + A \rightarrow [\ddot{D} \frown A] \rightarrow D^+ + A^-$$
$$\textit{Scheme I}$$

A simple general quantum mechanical theory of a 1:1 or an n:1 interaction of an electron donor with an electron acceptor has been proposed for the formation of the charge transfer complex. In the ground state, the two molecules are held together when they are in close proximity by forces such as van der Waals, dispersion, and hydrogen forces. Additional forces are contributed by the transfer of a small amount of charge from the donor to the acceptor. When a complex absorbs light of a suitable energy, it is raised from the ground state to the excited state. In this state, an electron that was shifted only slightly toward the acceptor is almost completely transferred. Therefore, the transfer of an electron by absorption of energy is responsible for the purple color of the formed complexes with maximum absorption at 515 nm for complexed naphazoline, 550 nm for complexed clemizole, 560 nm for complexed penicillin G sodium, and 540 nm for complexed piperazine.

Because the reaction of chloranil is known to be slow (29, 30, 32), the effect of time and temperature on the development of complexes was investigated. Maximum absorbance for the colored complexes was attained on leaving the reactant mixture in a thermostated water bath at 40° for 45 min (1), at 25° for 30 min (II), at 40° for 15 min (III), and at 60° for 10 min (IV). The complexed compounds gave absorbances that were unchanged for at least 1 hr (Fig. 1).

The slopes of the calibration curves reflect the sensitivity of the color attributed to charge transfer complex formation. The highest slope for naphazoline parallels its greatest basicity (pKa = 10.9) (34).

The other compounds, having lower pKa values, gave lower slopes compared to naphazoline. This finding indicates that the sensitivity of the developed color increases with increasing ability of the nitrogen atom to donate one of its lone pair of electrons. In penicillin G sodium (pKa = 2.8) (34), the presence of the carboxylic group and the amino group renders the compound of dual character and, therefore, gave the complex of the lowest slope.

A more detailed examination was made for the most sensitive compound, naphazoline. The decrease in absorbance per hour for complexed naphazoline followed zero-order kinetics, as determined by measuring the absorbance of the complex at 1-hr intervals for 5 hr. A plot of concentration (C, expressed in gram percent), calculated from the calibration graph, as a function of time (t, expressed in hours) gave a line with a slope

of $-K$. The K value was determined to be 0.000528, which indicated that the color was fading at a constant rate of 0.000528/hr.

Using Job's method of continuous variation (35), the ratio of naphazoline to chloranil equaled 1:1 (Fig. 2). This finding was anticipated by the presence of one basic or electron-donating center in the naphazoline molecule.

The absorbance of the naphazoline–chloranil complex was used to calculate the association constant using the Benesi–Hildebrand equation (36):

$$\frac{[A_0]}{A_\lambda^{AD}} = \frac{1}{\epsilon_\lambda^{AD}} + \frac{1}{K_c^{AD}\epsilon_\lambda^{AD}}\frac{1}{[D_0]} \qquad \text{(Eq. 1)}$$

where $[A_0]$ and $[D_0]$ are the total concentrations of the interacting species, A_λ^{AD} and ϵ_λ^{AD} are the absorbance and molar absorptivity of the complex at 515 nm, and K_c^{AD} is the association constant of the complex. On plotting the values of $[A_0]/A_\lambda^{AD}$ *versus* $1/[D_0]$, a line was obtained (Fig. 3) that is described by the following regression equation:

$$\frac{[A_0]}{A_\lambda^{AD}} = 2.0095 \times 10^{-6} + \frac{1}{[D_0]}(3.1868 \times 10^{-8}) \qquad \text{(Eq. 2)}$$

for which the regression coefficient equals 0.9997. The intercept of this line with the ordinate is $(\epsilon_\lambda^{AD})^{-1}$, and the slope equals $(\epsilon_\lambda^{AD} K_c^{AD})^{-1}$. From Eq. 2, the association constant equals 63.06. The standard free energy change (37), $\Delta G°$, of complexation is related to the association constant by:

$$\Delta G° = -2.303RT \log K \qquad \text{(Eq. 3)}$$

from which $\Delta G°$ equals -2.454 kcal.

The standard calibration graphs for naphazoline, clemizole, penicillin G sodium, and piperazine were constructed by plotting absorbance *versus* concentration (milligrams per 100 ml) calculated after addition of the chloranil solution. Conformity with Beer's law was evident in the concentration ranges of 1–5 mg % of naphazoline, 2–9 mg % of clemizole, 10–60 mg % of penicillin G sodium, and 2.5–12.5 mg % of piperazine.

Regression equations, derived using the method of least squares (38), for naphazoline, clemizole, penicillin G sodium, and piperazine are, respectively:

$$A_{515} = 0.0112 + 0.1960C \qquad \text{(Eq. 4)}$$

$$A_{550} = 0.0045 + 0.0920C \qquad \text{(Eq. 5)}$$

$$A_{560} = -0.0103 + 0.0166C \qquad \text{(Eq. 6)}$$

$$A_{540} = -0.0279 + 0.0684C \qquad \text{(Eq. 7)}$$

for which the respective regression coefficients are 0.9988, 0.9977, 0.9997, and 0.9979.

The validity of the regression equations was assessed in the determination of naphazoline in eye drops, clemizole in tablets, penicillin G sodium in vials, and piperazine in powder.

With the exception of clemizole, which was assayed by nonaqueous titration (Table I), the official methods were applied for the assay of the test compounds in powdered form (piperazine) or in dosage forms
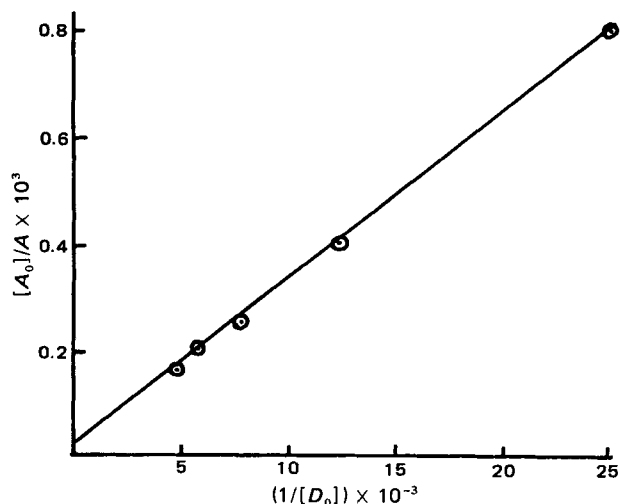

Figure 3—*Benesi–Hildebrand plot for naphazoline–chloranil complex in chloroform.*

Table I—Assay Results for Dosage Forms of Naphazoline, Clemizole, Penicillin G Sodium, and Piperazine

Preparation	Proposed Method[a]			Official Method[c]		
	n	Assumed Concentration[b], mg %	Mean ± SD, %	n	Assumed Concentration, mg%	Mean ± SD, %
Naphazoline drops[d]	4	2.40	99.89 ± 0.31 (0.71)	5	400.0	99.98 ± 0.56 (0.08)
Clemizole tablets[e]	4	4.00	100.46 ± 0.93 (0.99)	5	400.0	99.78 ± 0.46 (1.07)
Penicillin G sodium vial[f]	6	30.00	100.95 ± 1.51 (1.54)	5	12.0	100.43 ± 0.95 (1.0)
Piperazine powder[g]	5	6.25	100.52 ± 0.85 (1.37)	5	150.0	100.39 ± 0.79 (1.10)

[a] Percent recovery in the case of naphazoline and piperazine and percent of nominal concentration in the case of the other compounds. [b] Calculated in the final dilution after the addition of chloranil. [c] Clemizole is not official in BP 1973; thus, it was assayed, as with naphazoline, by nonaqueous titration; penicillin G sodium was assayed by iodometry (2), and piperazine was assayed by nonaqueous titration (3). [d] Prepared according to Martindale (34) and contained 50 mg % of naphazoline hydrochloride. The amount of salt can be calculated from the amount of base multiplied by 1.1738. [e] Obtained commercially as Allercur tablets from Chemical Industries Development Co. (batch 641), average weight 0.19 g. Each tablet contains 20 mg of clemizole hydrochloride; the salt can be calculated by multiplying the base concentration by 1.1122. [f] Obtained commercially; each vial is stated to contain 500,000 units; 1 mg of penicillin G sodium reference standard equals 1667 units (3). [g] Analyzed powder obtained from Alexandria Co. for Pharmaceutical and Chemical Industries. The values in parentheses are calculated t values for which the theoretical values at $\alpha = 0.05$ are: for df 3, 3.182; for df 4, 2.776; and for df 5, 2.571.

(naphazoline and penicillin G sodium). The results obtained are presented in Table I. The performance of the proposed method was judged through calculation of the t value. At the 95% confidence level, the calculated t value did not exceed the theoretical value. Therefore, the proposed method, as with the official method, gives assay results not significantly different from the true value. This finding indicates that the methods are equally accurate.

Compared to the official methods, the proposed procedure is simpler, faster, and more sensitive. These advantages encourage its application in the analysis and quality control of drugs.

Other drugs with basic centers are expected to give similar chromophores. Amino acids and proteins also give sensitive responses (32).

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