of excellent quality using special, flat oval, engraved punches.

The criteria used in evaluating the tablets were appearance, distribution of active ingredient, weight uniformity, friability, binding, sticking, capping, hardness, disintegration time, dissolution rates, and the effects of elevated temperatures, high humidity, and sunlight. No attempt was made to control the relative humidity during compression which took place over a period of approximately 2 months.

The data in Table I show excellent tablet weight uniformity. Table II shows that the active material was uniformly distributed and that no separation occurred during a 3-day compression period. Table III shows that the dissolution rates in simulated gastric fluid were not affected by high temperature. In simulated intestinal fluid the tablets disintegrated in 3–4 min., but the dissolution rates were slow due to poor solubility of the active compound at pH 7.5 (0.06 mg./ml.). Table IV shows that the tablets were not affected chemically or physically by high temperature, high humidity, and direct sunlight. Assays not reported here on tablets exposed to sunlight and high humidity showed good stability. The tablet color did not change significantly after 12 weeks at 50°. A very slight off-white color developed which could be detected only when the room temperature and the 50° samples were observed together.

SUMMARY

1. Placebo and active tablets were made by direct compression using anhydrous lactose U.S.P. XVII, tablet grade, as a diluent.

2. A placebo batch of approximately 500,000 tablets was run at a speed of 3500 tablets/min. on a Stokes 551 tablet machine resulting in excellent tablets. Special $^{9}/_{32}$-in. flat beveled edge, engraved punches were used.

3. Four batches of 200,000 tablets each, containing 0.5, 1, 2, and 5 mg. active material per tablet, were made using a set of four special, flat oval, engraved punches, on a stokes B-2 tablet machine at a speed of 44 r.p.m.

4. The placebo and active tablets were excellent as shown by the elegance, small tablet weight variation, uniform distribution of the active ingredient, fast disintegration and dissolution rates, good hardness, low friability, and lack of binding, sticking, and capping.

5. No induced feeding and/or metered hoppers were required.

6. Physical and chemical stability studies showed that high temperature, high humidity, and direct sunlight had no effect on the formulations.

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Notes

Quantitative Determination of Iodochlorhydroxyquin by Infrared Analysis

By T. URBÁNYI, D. SLONIEWSKY, and F. TISHLER

A quantitative infrared procedure for the determination of iodochlorhydroxyquin and its intermediates is described. The method is based on measurements of absorption in the 14.4 and 14.9 μ regions of a carbon disulfide solution of the compound. By measurements at other wavelengths in the infrared region, 5,7-diiodo-8-hydroxyquinoline, 5-chloro-8-hydroxyquinoline, and 5,7-dichloro-8-hydroxyquinoline, present as impurities, can also be quantitatively determined.

THE OFFICIAL U.S.P. XVII procedure (1) for the determination of iodochlorhydroxyquin, based on halogen content, suffers from the fact that the method frequently does not distinguish between the parent compound and its intermediates, which may occur as contaminants. The thin-layer chromatographic procedure of Korzun, Brody, and Tishler (2) offers a semiquantitative method for the determination of iodochlorhydroxyquin; however, 5,7-dichloro-8-hydroxyquinoline, which was found in many of the commercial samples examined, cannot be separated from iodochlorhydroxyquin by this method. Until now, phase solubility has been the only quantitative technique available for determining the absolute purity of iodochlorhydroxyquin. This procedure, although accurate and specific, is time consuming.

Bigeard *et al.* (3) have recently developed an infrared spectrophotometric method for the semiquantitative determination of iodochlorhydroxyquin

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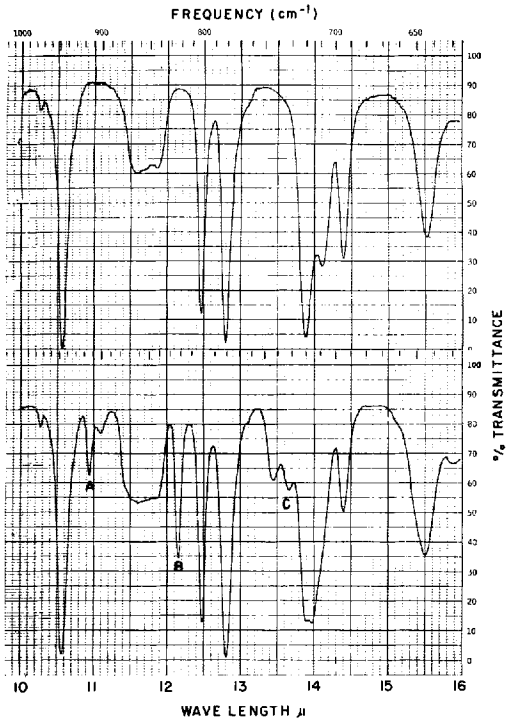

Fig. 1.—Infrared spectrum of iodochlorhydroxyquin (upper curve). Iodochlorhydroxyquin adulterated with: A, 5,7-diiodo-8-hydroxyquinoline; B, 5-chloro-8-hydroxyquinoline; C, 5, 7-dichloro-8-hydroxyquinoline (lower curve).

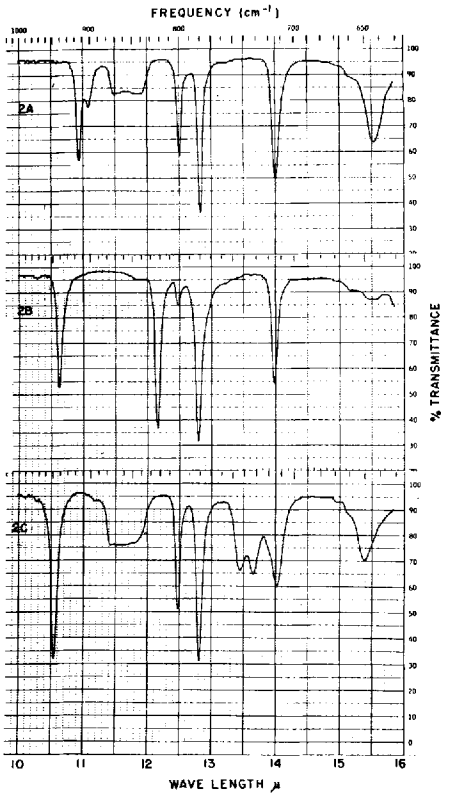

Fig. 2.—Infrared spectrum of: 2A, 5,7-diiodo-8-hydroxyquinoline; 2B, 5-chloro-8-hydroxyquinoline; 2C, 5,7-dichloro-8-hydroxyquinoline.

and its intermediates. The method, however, not only suffers from the typical experimental problems which arise in the potassium bromide disk technique, but also requires an infrared spectrophotometer capable of measurements in the far infrared region.

The modified infrared method described below fulfills the desired requirements for an analytical method—namely, specificity, rapidity, accuracy, and precision.

EXPERIMENTAL

All compounds used in this study were pure as determined by either phase solubility or by thin-layer chromatography. The infrared spectra were recorded on a Beckman I.R. 5 spectrophotometer and a Perkin-Elmer I.R. 621 spectrophotometer using reagent grade carbon disulfide as the solvent.

A calibration curve for the iodochlorhydroxyquin was prepared by dissolving various concentrations (2–10 mg./ml.) of the compound in carbon disulfide. The per cent transmittance at 14.4 and 14.9 μ was determined *versus* a carbon disulfide blank using 3-mm. cells equipped with sodium chloride plates. The ratios $[(T_{14.4\ \mu}/T_{14.9\ \mu}) \times 10]$ were calculated and the values plotted on the ordinate axis of 1-cycle semilogarithmic paper *versus* concentration. In a similar manner, calibration curves were prepared for 5,7-dichloro-8-hydroxyquinoline $[(T_{13.45\ \mu}/T_{15.25\ \mu}) \times 10]$, 5-chloro-8-hydroxyquinoline $[T_{12.15\ \mu}/TA\mu) \times 10]$,[1] and 5,7-diiodo-8-hydroxyquinoline $[(T_{10.95\ \mu}/TB\mu) \times 10]$.[1] A 0.5% solution of the sample in carbon disulfide was used in the spectrophotometric analysis of the synthetic mixtures and commercial samples. The phase solubility analyses were carried out in a nitrogen atmosphere using redistilled benzene as the solvent (4).

[1] A and B represent the transmittance readings at wavelengths 12.15 and 10.95 μ which are determined by the base line technique for the respective compounds.

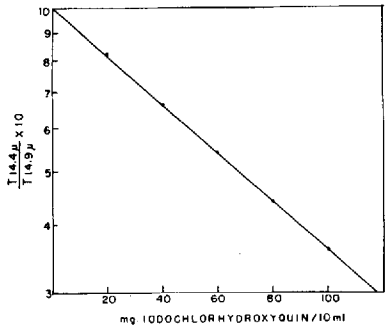

Fig. 3.—Linearity plot for iodochlorhydroxyquin.

DISCUSSION

A qualitative infrared examination of samples of iodochlorhydroxyquin U.S.P. currently on the market indicated the presence of the following impurities: 5,7-diiodo-8-hydroxyquinoline, 5,7-dichloro-8-hydroxyquinoline, and 5-chloro-8-hydroxyquinoline.

TABLE I.—ANALYSIS OF SYNTHETIC MIXTURES USING THE BECKMAN I.R. 5

Compd.	Mixture 1		Mixture 2	
	Added, %	Found, %	Added, %	Found, %
5-Chloro-8-hydroxyquinoline	3.0	2.85	5.0	5.2
5,7-Dichloro-8-hydroxyquinoline	3.0	2.80	5.0	5.0
5,7-Diiodo-8-hydroxyquinoline	3.0	2.70	5.0	5.5
Iodochlorhydroxyquin	91.0	89.0	85.0	84.0

TABLE II.—COMPARISON OF INFRARED AND PHASE SOLUBILITY METHODS

Manufacturer	Iodochlorhydroxyquin Content		
	I.R. 5, %	I.R. 621, %	Phase Solubility, %
Synthetic mixture[a]	89	90	90
A[b]	97	99	100
B	96	97	98
C[c]	60[d]	...	70
D	38	...	38
E	30	...	...

[a] Synthetic mixture contains 9% impurity. [b] Samples A and B are typical production batches prepared at Summit, N. J., and Basle, Switzerland. [c] Samples C, D, and E represent material sold as U.S.P. iodochlorhydroxyquin. [d] Insoluble material present.

5-Iodo-8-hydroxyquinoline was not observed in any samples and is not considered to be an important contaminant. The same technique described below can be used, however, for its determination.

The infrared spectrum between 10 and 16 μ for phase solubility pure iodochlorhydroxyquin is shown in the upper curve of Fig. 1. A sample of pure iodochlorhydroxyquin adulterated with 20%, 5,7-dichloro-8-hydroxyquinoline, 10% 5-chloro-8-hydroxyquinoline, and 20% 5,7-diiodo-8-hydroxyquinoline is shown in the lower curve of this figure. The infrared spectra of the three intermediates, 5,7-diiodo-8-hydroxyquinoline (2A), 5-chloro-8-hydroxyquinoline (2B), and 5,7-dichloro-8-hydroxyquinoline (2C) are shown in Fig. 2. It is quite obvious from Fig. 1 that the intermediates have a great effect on the spectrum of the pure material, especially at 10.95 μ (diiodo-), 12.15 μ (monochloro-), 13.45 μ (dichloro-), and 14.4 μ (iodochlorhydroxyquin).

Examination of the spectra of solutions of iodochlorhydroxyquin shows that the intensity of the absorption band occurring at 14.4 μ decreases as the amounts of impurities present increase. It can be seen from Fig. 2 that the three intermediates exhibit no significant absorption at this wavelength. Semilogarithmic plots of the ratio of per cent transmittance at 14.4 μ/per cent transmittance at 14.9 μ *versus* concentration of iodochlorhydroxyquin are linear. Figure 3 shows this relationship. Although similar plots are not shown for the three intermediates, they also exhibited linearity.

Even though the plots are linear over a wide range of concentration, it was observed that the most reproducible results were obtained in the range of 40–60% transmittance. It was found that samples containing these intermediates in substantial amounts were not soluble to the extent of 1% in carbon disulfide. They did give clear solutions, however, at a concentration of 0.5%. In order to maintain the absorption of the 14.4 μ band in the transmittance range of 40–60%, a light path of 3 mm. was employed.

In order to determine the accuracy of the procedure, synthetic mixtures were prepared and analyzed spectrophotometrically as described. The results appear in Table I.

Samples of U.S.P. quality iodochlorhydroxyquin from various commercial sources were analyzed using a Beckman I.R. 5 spectrophotometer and a Perkin Elmer I.R. 621 spectrophotometer. These results were compared with phase solubility analyses and are shown in Table II.

It can be seen from Table II that the accuracy of the method is increased if a more accurate and better resolving infrared spectrophotometer is used. In the case of the I.R. 5 spectrophotometer the accuracy is ±3% and with the I.R. 621 spectrophotometer, ±1%.

Analysis of samples C, D, and E by the current U.S.P. XVII procedures for chlorine and iodine and identity showed that two of the three samples passed all tests and could be considered of U.S.P. quality, even though they contain 60% or less of iodochlorhydroxyquin as determined by infrared measurements.

Since it has been demonstrated that iodochlorhydroxyquin may contain considerable amounts of intermediates as impurities and still meet present U.S.P. specifications, it is apparent that a more specific method of determination of purity of iodochlorhydroxyquin is necessary. The infrared procedure described provides a rapid, highly specific, and quantitative method for this purpose.

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