the results of 10 sample solutions (5 ml), each with a sparteine concentration of 0.005 *M*. The mean titer was 5.02 ml, with a standard deviation of 0.05 ml. The relative error was ~2% when 5 ml of diphenhydramine solution was titrated according to the procedure.

Commercial products containing diphenhydramine (injection, 10 mg/ml; tablet, 90 mg/g; and ointment, 10 mg/g) were analyzed according to the proposed method and a spectrophotometric method (8). The results were 9.97, 91.0, and 9.90 mg of diphenhydramine/ml in the injection, tablet, and ointment, respectively, by the proposed method and 9.95, 90.7, and 9.87 mg/g, respectively, by the spectrophotometric method. Tablet samples were dissolved in dilute sulfuric acid. The solution was filtered with a glass filter. Ointment samples were dispersed with 15 ml of ether in a separator. The contents were extracted three times with 10-ml portions of 0.1 *N* H_2SO_4. The extracts were neutralized slightly with 0.1 *N* NaOH solution.

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Measurement of Pseudoephedrine Hydrochloride Dissolution Using Chloride-Ion Electrode

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Abstract □ Experiments were performed to determine the suitability of using a chloride-ion electrode for the measurement of pseudoephedrine hydrochloride dissolution from commercially available compressed tablets. Dissolution experiments were carried out in 500 ml of distilled water using the USP paddle method at 100 rpm. Both chloride ion and pseudoephedrine (UV spectrophotometry) were measured at six different sampling times. Percent dissolved *versus* time values were linearized on a log-normal probability basis. The slopes of individual lines obtained from the chloride and pseudoephedrine measurements were compared using a Student *t* test and did not differ significantly ($t = 0.415$, $df = 5$, $p > 0.05$). In addition to providing an efficient, inexpensive, and simple method for measuring pseudoephedrine hydrochloride dissolution rates, the chloride-ion electrode could be used in the measurement of dissolution rates for a wide variety of drugs available as hydrochloride salts.

Keyphrases □ Pseudoephedrine hydrochloride—measurement of dissolution using chloride-ion electrode □ Chloride-ion electrode—measurement of pseudoephedrine hydrochloride dissolution □ Dissolution—pseudoephedrine hydrochloride, measurement using chloride-ion electrode

There has been a significant increase in the use of dissolution rate testing for the development of new dosage forms as a quality assurance tool and as a predictor of bioavailability in instances where successful *in vivo–in vitro* correlations have been established. Recent activity has centered on the establishment of automated procedures and the optimization of existing methodology with emphasis on the USP rotating-basket and USP paddle methods (1). One interesting aspect has been the automation of analytical measurements, mainly through the use of flow-through cells in conjunction with various spectrophotometers (2–7). Another analytical procedure that lends itself to automation is the use of a specific ion electrode to measure directly the drug's counterion in the dissolution flask.

BACKGROUND

A survey of the recent literature revealed limited use of selective ion electrodes for measurement of tablet or capsule dissolution rates. Mason *et al.* (8) described the use of a sodium-ion selective electrode for the measurement of dissolution rates of specially prepared sodium salicylate tablets. They found agreement between sodium-ion concentrations measured by the selective ion electrode and atomic absorption spectrophotometry. Sodium-ion concentrations agreed with salicylate concentrations measured spectrophotometrically. The method was later extended (9) to measure dissolution rates of commercial tablets containing warfarin sodium, butabarbital sodium, and sodium bicarbonate. Data obtained by selective ion electrode and spectrophotometric measurements were in agreement when both methods were utilized.

Thomas (10) used a potassium-ion specific electrode to study the release rate of potassium from several brands of slow-release potassium chloride tablets. Other investigators (11), using similar methodology, also studied the dissolution release pattern of sustained-release potassium chloride tablets. This report presents the results of similar studies using anion measurements; *i.e.*, a chloride-ion electrode was used to measure the dissolution rate of commercial pseudoephedrine hydrochloride tablets.

EXPERIMENTAL

Materials—Pseudoephedrine hydrochloride tablets[1] (60 mg/tablet) and pseudoephedrine hydrochloride[2] were used as received. An ionic strength adjuster (5 *M* $NaNO_3$) was prepared by dissolving 42.5 g of sodium nitrate[3] in 100 ml of distilled water.

Chloride-Ion Measurements—Chloride ions were detected by a chloride-ion electrode[4] together with a double-junction electrode[5]. The electrodes were connected to an analyzer[6], which displayed direct millivolt readings of the measured potentials.

A calibration curve was constructed for pseudoephedrine hydrochloride. Standard solutions of 0.01–1.00 mg/ml were prepared. For each standard solution, 100 ml of solution and 2 ml of ionic strength adjuster were poured into a 150-ml glass beaker and thoroughly stirred. The millivolt reading was recorded once the reading stabilized. These values were then linearized by plotting them on a linear scale as a function of the logarithm of the chloride concentration.

UV Spectrophotometric Measurements—A Beer's law curve was constructed for pseudoephedrine hydrochloride in distilled water. The

[1] Sudafed tablets, batches 7L2089 and 7L2087, Burroughs Wellcome Co., Research Triangle Park, N.C.

[2] Batch P5705-4G, Burroughs Wellcome Co., Research Triangle Park, N.C.

[3] ACS reagent, Fisher Scientific, Pittsburgh, Pa.

[4] Model 94-17A, Orion Research, Cambridge, Mass.

[5] Model 90-02, Orion Research, Cambridge, Mass.

[6] Microprocessor Ionlyzer/901, Orion Research, Cambridge, Mass.

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Table I—Mean [a] (± *SEM*) Percent of Drug Dissolved from Two Separate Batches of 60-mg Pseudoephedrine Hydrochloride Tablets Analyzed by Chloride-Ion Measurement and UV Spectrophotometry

Minutes	Batch 7L2089		Batch 7L2087	
	Chloride Ion	UV Spectrophotometry	Chloride Ion	UV Spectrophotometry
2	31.1 ± 1.2	31.3 ± 1.3	32.9 ± 3.8	29.5 ± 2.1
5	57.6 ± 1.8	60.9 ± 4.3	62.9 ± 6.3	49.2 ± 1.2
10	88.2 ± 1.7	81.8 ± 2.3	88.8 ± 4.6	76.2 ± 1.7
15	98.3 ± 0.5	93.8 ± 2.0	96.4 ± 1.4	92.1 ± 1.8
30	99.9 ± 0.1	99.0 ± 0.7	99.4 ± 0.2	99.3 ± 0.3
60	99.8 ± 0.2	98.2 ± 0.7	99.8 ± 0.2	99.3 ± 0.4

[a] $n = 6$.

absorbances of the standard and sample solutions were read at a wavelength of 257 nm[7].

Dissolution Studies—Dissolution studies were performed using the USP rotating-paddle method (1) at a stirring rate of 100 rpm. The dissolution medium consisted of 500 ml of distilled water and 10 ml of ionic strength adjuster for chloride-ion measurements. The ionic strength adjuster was omitted when UV measurements were made.

For measurements of chloride-ion concentrations, the electrodes were placed in the flask 5 cm from the bottom to permit direct measurement without sample withdrawal. Ten-milliliter samples were withdrawn with replacement and filtered through 0.65-μm membrane filters[8] for UV measurements. Direct readings and sample withdrawal were done at 2, 5, 10, 15, 30, and 60 min. These experiments were performed on two different batches of tablets. Six tablets from each batch were studied by each of the two analytical methods.

Measured concentrations were converted to amount dissolved, with correction for sample replacement where appropriate. The data was linearized using log-normal probability plots. The slopes of the resulting lines were statistically analyzed using a Student t test.

RESULTS AND DISCUSSION

The millivolt readings of the standard solutions were recorded on 3 consecutive days and indicated good reproducibility. A similar concentration range of standard solutions was prepared on 3 different days, and millivolt readings of each solution were recorded immediately after preparation with good reproducibility. A higher standard error of the mean (*SEM*) was observed at the 0.01-mg/ml concentration. Because the range of concentrations between 0.01 and 0.03 mg/ml was of minimal importance to the dissolution test, the calibration curve was established between 0.03 and 1.00 mg/ml and expressed as:

$$V = 125.62 - 53.55(\log D) \qquad \text{(Eq. 1)}$$

where V is the potential (millivolts), D is the drug concentration (milligrams per milliliter). Linear correlation coefficient (r) was 0.996.

Dissolution test results for both analytical methods are summarized in Table I for the two batches of 60-mg pseudoephedrine hydrochloride tablets. Although some differences existed at the 5-, 10-, and 15-min sampling times for both batches, no statistically significant differences were found between the dissolution rates as determined by the two methods at the 95% confidence level.

Initial attempts to use this method for the measurement of dissolution rates of sugar-coated 30-mg pseudoephedrine hydrochloride tablets resulted in large amounts (120–150% of label strength) of pseudoephedrine hydrochloride appearing in solution. Various experiments were conducted to determine the source of this considerable interference with the measurement of chloride ions. The results revealed that the major source was caused by certain unidentified ingredients in the coating material. These findings indicated that the chloride-ion electrode would be of limited use for obtaining dissolution rate profiles for such products. However, a standard could be established for the measurement of dissolution at a single time point as a quality assurance procedure.

The results of these studies demonstrate that use of a chloride-ion electrode is a rapid and effective way of generating dissolution data provided that interferences are minimal. Although this report is limited to a single drug, the method may have application for other drugs available as hydrochloride salts.

[7] Model 35 recording spectrophotometer, Beckman Instruments, Irvine, Calif.
[8] Millipore Corp., Bedford, Mass.

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