in the tablet. This results in weaker points within the tablets and fine cracks around the agglomerates. Higher tablet friability and higher tablet-to-tablet variability in dissolution could be explained as resulting from clumping of starch grains and weaker points around these agglomerates. The cross-sectional view of the tablet compressed from granules containing starch in the wet-granulation stage is shown in Fig. 8. No clumping of the starch grains was seen. The materials were well distributed in the tablet matrix. Comparisons of the two punch tip geometries revealed no major differences in the distribution of starch resulting from the differential particle movement during compression (compare Figs. 5 and 6 with Figs. 7 and 8).

Figure 9 gives cross-sectional views of the placebo tablet compressed with the standard concave punches (formulation B). Tablets containing dry-blended starch showed only a few starch grains (Fig. 9A) compared with the largely fused lactose (Fig. 9B) for tablets compressed from wet-granulated starch.

The cross-sectional views of the tablets compressed from formulation C without a wet binder are shown in Fig. 10. Similar to ticlopidine hydrochloride tablets, clumping of starch grains was observed when starch was dry blended (Fig. 10A and B). Starch grains do not adhere to themselves or to the other materials in the tablet. This is in contrast to the case when starch was wet granulated with other excipients using water (Fig. 10C and D). Agglomerates or even isolated starch grains were not observed. The starch was well embedded in the soluble excipient, lactose, which on drying crystallized out.

In conclusion, this study suggests that the tablet friability and *in vitro* dissolution improved by incorporating starch in the wet-granulation stage of formulations containing a soluble drug and/or a soluble major excipient. This improvement in tablet friability and *in vitro* dissolution is due to a better bonding, fewer weak points, and better homogeneity of the disintegrator, starch, within the tablet.

## REFERENCES


(1) N. R. Patel and R. Hopponen, *J. Pharm. Sci.*, **55**, 1065 (1966).

(2) J. T. Ingram and W. Lowenthal, *J. Pharm. Sci.*, **57**, 393 (1968).

(3) W. Lowenthal and R. A. Burruss, *J. Pharm. Sci.*, **60**, 1325 (1971).

(4) W. Lowenthal, *J. Pharm. Sci.*, **61**, 455 (1972).

(5) W. Lowenthal and J. H. Wood, *J. Pharm. Sci.*, **62**, 287 (1973).

(6) Z. T. Chowhan, I.-C Yang, A. A. Amaro, L.-H. Chi, and Y. P. Chow, *J. Pharm. Sci.*, **71**, 1371 (1982).


# Application of the Ammonia Gas-Sensing Electrode: Determination of Drugs Having a Carbothionamido Group by Decomposition with Acid


**SHOICHIRO TAGAMI** ˣ **and HIROMI MAEDA**



Received April 19, 1982, from the *Toyama Medical and Pharmaceutical University, Sugitani, Toyama, Japan.* Accepted for publication August 4, 1982.



**Abstract** □ A method to determine drugs having a carbothionamido group using an ammonia gas-sensing electrode is described. To obtain analytical accuracy, the effect of factors that influence the potential is also discussed. Ethionamide or prothionamide was refluxed with 20% HCl to give ammonium chloride, hydrogen sulfide, and a carboxylic acid. The ammonia, which evolved at pH > 11, was determined. A linear calibration plot was obtained within the drug concentration range of $2 \times 10^{-5}$–$1 \times 10^{-2}$ *M*.



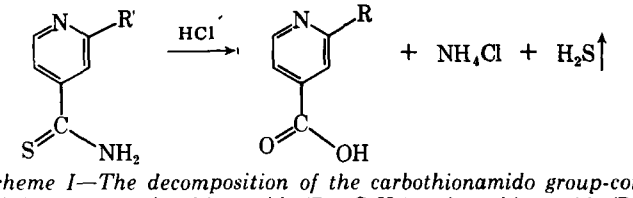
**Keyphrases** □ Ammonia gas-sensing electrode—determination of carbothionamido groups, acid decomposition of ethionamide and prothionamide □ Ethionamide—carbothionamido group, determination using ammonia gas-sensing electrode, acid decomposition □ Prothionamide—carbothionamido group, determination using ammonia gas-sensing electrode, acid decomposition


In recent years, the development of gas-permeable membrane electrodes has led to their widespread use in the analytical field (1). Although electrodes that use immobilized enzymes on the membrane are employed for the determination of organic and biological compounds, few applications to drug analysis have been reported in the literature, and no pharmacopeia has yet introduced their use for assays. Therefore, a previous paper (2) described procedures for the determination of drugs having a carboxyamido group (ethenzamide, niacinamide, pyrazinamide, and salicylamide).

The present paper describes the determination of drugs having a carbothionamido group in an analogous way and describes in detail the operations and handling of the ammonia gas-sensing electrode. The carbothionamido group decomposes into ammonium chloride, hydrogen sulfide, and a carboxylic acid on heating with hydrochloric acid (Scheme I). It may thus be possible to utilize the ammonia gas-sensing electrode to determine the ammonia derived from the ammonium chloride during the decomposition.

## EXPERIMENTAL

**Apparatus and Reagents**—Direct potentiometric measurements were made at 20° in an 80-ml cell equipped with a magnetic stirrer, using a pH/mV meter[1] with a recorder[2] and ammonia gas-sensing electrodes A[3] and B[4]. Ethionamide[5], prothionamide[6], and ammonium chloride[7] were analytical grade or certified quality and were dried *in vacuo* at room temperature for 5 hr. Other chemicals used were reagent grade. Ammonium chloride solutions of 0.001–1 *M* and ammonium chloride solutions of 0.01–0.1 *M* saturated with ammonium picrate were used as internal filling solutions.




*Scheme I—The decomposition of the carbothionamido group-containing compounds ethionamide ($R = C_2H_5$) and prothionamide ($R = C_3H_7$).*

[1] Model F-7ss, Hitachi-Horiba Instruments, Horiba Co., Kyoto.
[2] Model EPR-22A, Toa-Denpa Co., Tokyo.
[3] Model 5002-05T, Horiba Co., Kyoto.
[4] Model 95-10, Orion Research Inc., Cambridge.
[5] Daiichi Seiyaku Co., Tokyo (lot CA 7921806).
[6] Lederle Japan Ltd., Tokyo (lot CA 7917603; assay, 100.2%).
[7] E. Merck, Darmstadt (lot 0074534; assay, 99.8%).




0022-3549/83/0900-0988$01.00/0

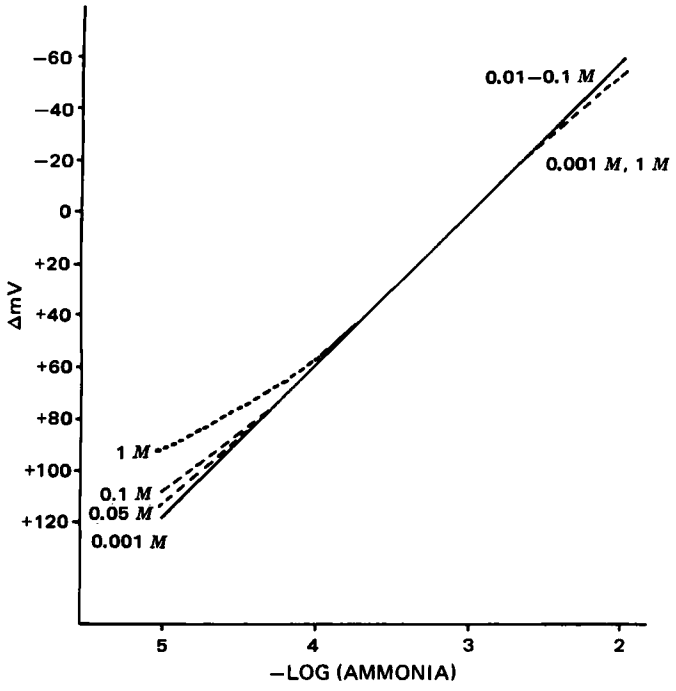



**Figure 1**—*Effect of internal filling solutions on the calibration plot.*

**Standard Solution**—To 25 ml of 0.1 *M* ammonium chloride solution in a 250-ml volumetric flask was added 50 ml of a 20% HCl solution which had been neutralized to pH 6.5 with sodium hydroxide, and the resulting solution was diluted to volume with distilled water. A working solution was prepared by diluting this stock solution to $1 \times 10^{-2}$ *M* ammonium chloride.

**Decomposition of Drugs**—A mixture of 166.24 mg ($1 \times 10^{-3}$ mole) of ethionamide or 180.27 mg ($1 \times 10^{-3}$ mole) of prothionamide and 20 ml of 20% HCl was heated at reflux in an oil bath for 1 hr. The solution was cooled, poured into a 100-ml beaker, and diluted with ~50 ml of water. A drop of methyl orange was added while cooling the beaker continuously, and the acid was cautiously neutralized with 10 *N* NaOH solution until the indicator began to change color. The solution was then adjusted to pH 6.5 with dilute sodium hydroxide solution using a pH meter. The solution was poured into a 100-ml volumetric flask and diluted to volume with water. The concentrations of the final drug solutions were $1 \times 10^{-2}$ *M*, corresponding to $1 \times 10^{-2}$ *M* ammonia. Sample solutions for measurements were obtained by dilution of these solutions with water.

**Assay Procedure**—A 50-ml portion of the sample and standard solutions used was incubated for 30 min at 20°, and 1 ml of 5 *N* NaOH was added before the electrode was immersed in the solutions. (After alkalinization, the solutions are stable for several hours in the cell with a rubber stopper.) The standard procedure was as follows: The electrode with 0.05 *M* ammonium chloride internal filling solution was washed with water and immersed for ~5 min in fresh 0.05 *M* NaCl solution acidified with dilute hydrochloric acid at pH 4, and then the old internal filling solution was replaced with fresh 0.05 *M* ammonium chloride solution. The electrode was placed in the first standard, and the potential was measured. After washing the electrode as described above, the electrode was placed in the sample solution, and the potential was measured. After another washing, the electrode was placed in the second standard, and the potential was measured. The sample concentration was determined from the calibration curve.

**Assay of Tablets**—Twenty tablets were weighed and finely powdered. A portion of the powder (equivalent to ~166.24 mg of ethionamide or 180.27 mg of prothionamide) was accurately weighed, and 20 ml of acetone was added. The solution was stirred and then centrifuged. The supernatant acetone solution was removed, and 20 ml of acetone was added to the residue. The extraction procedure was repeated until the supernatant acetone solution was colorless. The acetone fractions were evaporated to dryness, and the resulting residue was refluxed for 1 hr with 20 ml of 20% HCl. As described above, the acidic solution was adjusted to pH 6.5 and diluted to 250 ml in a volumetric flask. The ammonia concentration in a 50-ml portion of the sample was determined from the calibration curve.

**Table I—Effect of Dissolved Salts on the Electrode Potential**

| Salt | Salt Concentration,[a] *M* | Potential Shift, mV |
|---|---|---|
| Sodium chloride | $1 \times 10^{-4}$ | 0 |
| | $1 \times 10^{-3}$ | 0 |
| | $1 \times 10^{-2}$ | +0.1 |
| | $1 \times 10^{-1}$ | −0.1 |
| | $5 \times 10^{-1}$ | −0.1 |
| | 1 | −0.6 |
| Potassium chloride | $1 \times 10^{-4}$ | +0.2 |
| | $1 \times 10^{-3}$ | −0.1 |
| | $1 \times 10^{-2}$ | −0.1 |
| | $1 \times 10^{-1}$ | −0.2 |
| | $5 \times 10^{-1}$ | −0.6 |
| | 1 | −2.2 |
| Sodium sulfate | $1 \times 10^{-4}$ | 0 |
| | $1 \times 10^{-3}$ | +0.1 |
| | $1 \times 10^{-2}$ | −0.1 |
| | $1 \times 10^{-1}$ | −1.0 |
| | $5 \times 10^{-1}$ | −4.0 |
| | 1 | −8.4 |
| Potassium sulfate | $1 \times 10^{-4}$ | +0.2 |
| | $1 \times 10^{-3}$ | +0.1 |
| | $1 \times 10^{-2}$ | 0 |
| | $5 \times 10^{-2}$ | −0.4 |
| | $1 \times 10^{-1}$ | −0.8 |
| | $3 \times 10^{-1}$ | −2.7 |
| | $5 \times 10^{-1}$ | −4.7 |

[a] The given salt concentrations are the concentrations in $1 \times 10^{-3}$ *M* ammonium chloride.

## RESULTS AND DISCUSSION

**Internal Filling Solution**—The electrolyte solution in the reference electrode and the internal filling solution contained known amounts of ammonium chloride. Commercially available ammonia gas-sensing electrodes differ slightly from one another in the concentration of the internal filling solution and in their inner structure. The electrolyte solution in reference electrode A can be replaced by fresh electrolyte solution, but not in electrode B. By using both electrodes, the effect of internal filling solutions on the calibration plot was investigated. First, electrode A, in which the internal filling solution and the electrolyte solution are the same, was examined by employing filling solutions with 0.001–1 *M* ammonium chloride. The results are shown in Fig. 1, where the potential difference (ΔmV) from $1 \times 10^{-3}$ *M* ammonia to each concentration of ammonia is plotted as the ordinate and the ammonia concentration is plotted as the abscissa. Using 0.1, 0.05, and 0.01 *M* filling solutions, a linear calibration plot was obtained for the concentration range of $1 \times 10^{-4}$–$1 \times 10^{-2}$ *M* ammonia. Using 0.001 *M* filling solution, a linear calibration plot was obtained at $1 \times 10^{-5}$–$1 \times 10^{-3}$ *M* ammonia.

**Table II—Determination of Drugs Having a Carbothionamido Group**

| Drug | Determination | Label Claim, mg | Found, mg | Recovery, % |
|---|---|---|---|---|
| Ethionamide | 1 | 0.831 | 0.829 | 99.8 |
| | 2 | 0.831 | 0.832 | 100.1 |
| | 3 | 0.831 | 0.832 | 100.1 |
| | 4 | 8.312 | 8.337 | 100.3 |
| | 5 | 8.312 | 8.320 | 100.1 |
| | 6 | 8.312 | 8.312 | 100.0 |
| | 7 | 8.312 | 8.304 | 99.9 |
| | 8 | 8.312 | 8.304 | 99.9 |
| Mean ± *SD* | | | | 100.03 ± 0.15 |
| Prothionamide | 1 | 0.901 | 0.900 | 99.9 |
| | 2 | 0.901 | 0.901 | 100.0 |
| | 3 | 0.901 | 0.898 | 99.7 |
| | 4 | 0.901 | 0.902 | 100.1 |
| | 5 | 9.014 | 9.014 | 100.0 |
| | 6 | 9.014 | 9.005 | 99.9 |
| | 7 | 9.014 | 9.050 | 100.4 |
| | 8 | 9.014 | 9.032 | 100.2 |
| Mean ± *SD* | | | | 100.03 ± 0.20 |

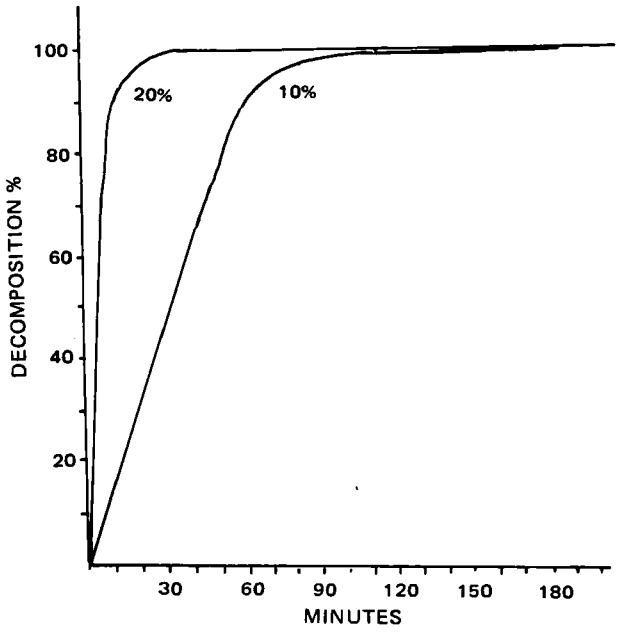



**Figure 2**—*Effect of hydrochloric acid concentrations on drug decomposition.*

The slope of the lines was 58 mV per decade increase in ammonia concentration. At a low concentration range of ammonia (from $1 \times 10^{-5}$ to $1 \times 10^{-4}$ *M*), the higher the concentration of the filling solution, the smaller ΔmV. At a high concentration range of ammonia (from $1 \times 10^{-3}$ to $1 \times 10^{-2}$ *M*), ΔmV became <58 mV when 0.001 *M* filling solution was used. With 1 *M* filling solution, the electrode potentials were unstable; the calibration plot was not linear, resulting in an S-curve. Based on the above data, 0.001 *M* filling solution is considered suitable for potential measurements of a low level of ammonia ($1 \times 10^{-5}$–$1 \times 10^{-3}$ *M*). In the concentration range of $1 \times 10^{-4}$–$1 \times 10^{-2}$ *M* ammonia, 0.01–0.1 *M* filling solutions are suitable for the potential measurements. However, with a high level of ammonia ($1 \times 10^{-3}$–$1 \times 10^{-2}$ *M*), the use of 0.1 *M* filling solution is preferred.

The electrolyte solution in electrode B consists of a saturated solution of ammonium picrate or ammonium purpurate. To provide a chloride concentration for the reference Ag–AgCl electrode, the electrolyte also contains a known amount of ammonium chloride (3). However, the concentration of ammonium chloride in this electrode is not obvious. Using an internal filling solution containing 0.05 *M* ammonium chloride saturated with ammonium picrate, a linear calibration plot was obtained in the concentration range of $1 \times 10^{-4}$–$1 \times 10^{-2}$ *M* ammonia, and the potential difference (ΔmV) was 58 mV per decade increase in ammonia concentration. However, using 0.01 or 0.1 *M* ammonium chloride saturated with ammonium picrate, the calibration plot was not linear.

On using the Instrumental Laboratory filling solution, a linear calibration plot was obtain in the ammonia concentration range of $1 \times 10^{-4}$–$1 \times 10^{-2}$ *M*. This indicates that the Instrumental Laboratory solution and the 0.05 *M* ammonium chloride solution saturated with ammonium picrate are the same.

**Standard Solution**—Water vapor resulting from the difference in concentrations of ions between the decomposition and internal filling solutions (osmotic strength) leads to error, and the partial pressure of the dissolved gas is also a function of the sample temperature and the level of dissolved species (4). In the present study, therefore, the effect of dissolved salts on the potential was examined more closely. The results are shown in Table I. In a given $1 \times 10^{-3}$ *M* ammonium chloride solution, $1 \times 10^{-1}$ *M* potassium or sodium sulfate caused an ~1-mV electrode shift. However, in sodium chloride, the amount of salt is negligibly small in a concentration <1 *M*. The experimental data indicated that the calibration plot of ammonium chloride standard solution coincided with that of the decomposition solution in the concentration range of $1 \times 10^{-4}$–$1 \times 10^{-2}$ *M*. Thus, the standard solution should use ammonium chloride standard instead of the drug standard.

To obtain analytical accuracy, a calibration curve should be prepared for every set of determinations. Since the potential of the glass electrode is stable for ~12 hr, but changes with after that time, the slope of the linear calibration plot is not constant.

**Electrode Response**—The response of the electrode is a function of the ammonia concentration, with a faster response at higher ammonia levels. In a given ammonia concentration it is also a function of the salt concentration, with a faster response at higher dissolved salt levels. On repeated use, the equilibrium time may become longer because of deterioration of the glass electrode. To activate the electrode, the electrode tip should be immersed in 2% ammonium fluoride for 3 min, then in 5 *N* HCl for several minutes, followed by exhaustive washing with water.

Another important factor that influences the electrode response is the working area of the gas-permeable membrane. Employing membranes with diameters of 4 $mm^3$ and 9 $mm^4$, the response times of the electrode were found to be 20–30 min and 1–3 min in $1 \times 10^{-3}$ *M* ammonia, respectively.

When the electrode is immersed in water for storage overnight, the response time may become longer, as water vapor may condense in the hole in the gas-permeable membrane, hindering the passage of ammonia gas. For storage overnight or over the weekend, the electrode tip should be immersed in ammonium chloride solution, with the same level of ammonium chloride as in the internal filling solution to avoid wetting and change of internal filling solution concentration.

**Contamination**—The electrode is always contaminated by the ammonia adsorbed on the gas-permeable membrane and by the ammonia in the small gap between the bottom cap of the electrode and the gas-permeable membrane. Since the contaminating substance cannot be removed by washing with water, the electrode tip must be washed by immersion in freshly prepared sodium chloride solution (pH 4) of a similar concentration to the ammonium chloride in the internal filling solution. At a concentration $<10^{-4}$ *M* ammonia, the potential change resulting from contamination is much larger than in the concentration range of $10^{-3}$–$10^{-2}$ *M*. The electrode tip must be washed thoroughly. During washing of the electrode, the concentration of the internal filling solution is slightly changed. Thus, the internal filling solution should be replaced with fresh solution before making potential measurements.

**Reproducibility**—In a sample solution with a high level of dissolved salt, reproducibility is influenced by the mode of operation of the potential measurement. In the first procedure, after alkalinization of the sample solution with sodium hydroxide, the electrode is immersed in the sample solution and the potential measurements are determined. In the second procedure, following immersion of the electrode in the sample solution, the solution is alkalinized with sodium hydroxide after a few minutes, and then potential measurements determined. The potential values obtained by these different modes of operation are not equal. Results show that in the second procedure, the concentration of the internal filling solution changes with lapse of time due to water vapor caused by osmotic pressure. Small changes in the concentration of the filling solution influence the potential value. The potentiometric measurements should be determined using the first procedure.

Electrode B has a fast response time, but the large area of the gas-permeable membrane subjects it to influence from osmotic pressure. Therefore, electrode A was used.

**Decomposition of Drugs**—A mixture of ethionamide and 20% HCl was refluxed until complete decoloration had taken place. Hydrogen sulfide was evolved during the course of the reaction, and the yellow solution became colorless after 30 min. The resulting ammonia formed in the decomposition was determined at various times (Fig. 2). The electrode potential reached a maximum at a heating time of 30 min. In the case of decomposition with 10% HCl, the electrode potential reached a maximum at a heating time of 3 hr. After 1 and 2 hr, the recoveries were 87 and 99%, respectively. The decomposition time of prothionamide was the same

**Table III—Determination of Tablets**

| Drug | Determination | Label Claim, mg | Found, mg | Recovery, % |
|---|---|---|---|---|
| Ethionamide | 1 | 155.96 | 157.36 | 100.9 |
| | 2 | 166.24 | 167.07 | 100.5 |
| | 3 | 166.24 | 166.02 | 99.9 |
| | 4 | 164.34 | 165.29 | 100.6 |
| | 5 | 173.46 | 174.22 | 100.4 |
| Mean ± *SD* | | | | 100.46 ± 0.36 |
| Prothionamide | 1 | 187.00 | 187.94 | 100.5 |
| | 2 | 180.12 | 181.15 | 100.6 |
| | 3 | 205.54 | 206.07 | 100.3 |
| | 4 | 195.41 | 195.49 | 100.0 |
| | 5 | 182.35 | 183.63 | 100.7 |
| Mean ± *SD* | | | | 100.42 ± 0.28 |

as that of ethionamide. When the potential was plotted against the logarithm of the drug concentration, a linear calibration plot was obtained in the drug concentration range of $2 \times 10^{-5}$–$1 \times 10^{-2}$ $M$.

The amount of drug was first determined with the pure drug powder. According to USP XX (5), ethionamide contains ≥98.0% and ≤102.0% of $C_8H_{10}N_2S$, calculated on an anhydrous basis. Prothionamide is described only in the JP X (6), and not in the USP or British Pharmacopeia (7). According to the Japanese Pharmacopeia, prothionamide determined on a dry weight basis should be >98.0% pure.

The recovery of the drugs is shown in Table II. Determinations were performed on eight samples of both drugs. The amounts of ethionamide and prothionamide were estimated with the same average errors of 0.03%, and the standard deviations were 0.15 and 0.20, respectively. The recoveries were good and reproducible.

Determinations on both tablets were carried out. A suitable extraction solution was sought. Both drugs are very soluble in methanol and glacial acetic acid and are also soluble in ethanol and acetone; however, in the extraction it is necessary to avoid interference from extraneous compounds. Methanol is used in the USP procedure. The tablets were therefore extracted with methanol and after evaporation of the methanol, the residue was heated at reflux with 20% HCl. After heating for 3 hr, the solution became brown, and a brown precipitate separated out. Evidently the precipitate resulted from impurities dissolved in the methanol.

The tablets were then extracted with acetone. After dissolution in acetone, the solution was centrifuged. This was found to be the best method because filtration of the acetone solution proved to be difficult. The extraction was carried out four or five times until the extract was colorless. The solvent was evaporated, and the residue was heated at reflux for 1 hr with 20% HCl to give a light-brown precipitate and a pale-brown solution. The acidic solution was then neutralized with sodium hydroxide at pH 6.5, and the resulting mixture was subjected to potentiometric measurements. Determinations were performed on five samples of 20 tablets. According to the USP XX, ethionamide tablets contain ≥95.0% and ≤110% of the labeled amount of drug. The results obtained are shown in Table III. The mean recoveries for ethionamide and prothionamide tablets were 100.46 and 100.42%, respectively, and the respective standard deviations were 0.36 and 0.28. The labeled amount of drugs was 100 mg/tablet. The recoveries are given compared with the theoretical amount of ammonia in the drug tablets, and it is believed that one tablet indeed contains 100 mg.

## CONCLUSION

The assay method for the drugs in JP X is based on the nonaqueous titration method using perchloric acid; however, the color change is not sharp. In the BP, the end-point is determined potentiometrically, which alleviates this problem. In USP XX, a colorimetric method is used for the determination of the pure powder and tablets. The procedure is accurate, but nonspecific.

The proposed method for the assay of drugs having a carbothionamido group is simple and specific. The recovery is satisfactory and lies within acceptable limits. In view of this, use of the ammonia gas-sensing electrode is recommended as a possible pharmacopeial method.

## REFERENCES


(1) G. E. Baiulescu and V. V. Cosofret, "Applications of Ion-Selective Membrane Electrodes in Organic Analysis," Halsted Press (div. John Wiley & Sons), New York, N.Y., 1977.

(2) S. Tagami and M. Fujita, *J. Pharm. Sci.*, **71**, 523 (1982).

(3) J. H. Riseman and J. Krueger, U.S. Pat., 3,830,718 (1974).

(4) "Instruction Manual," Orion Research Inc., 1978, pp. 23 and 27.

(5) "The United States Pharmacopeia," 20th rev., U.S. Pharmacopeial Convention, Rockville, Md. 1980, p. 308.

(6) "The Japanese Pharmacopeia," 10th rev., Hirokawa Publishing Co., Tokyo, 1981, p. 1352.

(7) "The British Pharmacopeia," The University Printing House, Cambridge, England, 1973, p. 194.


## ACKNOWLEDGMENTS


The authors are grateful to Professor Takenori Tanimura for his unfailing guidance throughout the course of this work.


# Pharmacokinetics of Chlorzoxazone in Humans


**RAVI K. DESIRAJU ˣ, NED L. RENZI, Jr., RAMCHANDRA K. NAYAK, and KUNG-TAT NG**



Received March 5, 1982, from the *Department of Drug Metabolism, McNeil Pharmaceutical, Spring House, PA 19477.* Accepted for publication August 6, 1982.



**Abstract** □ Twenty-three normal male subjects received 900 mg of acetaminophen and 750 mg of chlorzoxazone as an oral suspension. Analysis of plasma samples indicated a rapid absorption and rapid elimination of chlorzoxazone. Average values of the elimination half-life and plasma clearance were 1.12 ± 0.48 hr and 148.0 ± 39.9 ml/min, respectively. Analysis of urine samples showed that chlorzoxazone was eliminated from the body as the glucuronide conjugate of the intermediate metabolite 6-hydroxychlorzoxazone, to the extent of 74% of the dose. The plasma and the urinary excretion data were fitted to theoretical equations, and excellent fits were obtained using a five-parameter pharmacokinetic model.



**Keyphrases** □ Chlorzoxazone—analysis in human plasma and urine, administration with acetaminophen; pharmacokinetics □ Pharmacokinetics—chlorzoxazone, analysis in human plasma and urine, concomitant administration with acetaminophen □ Acetaminophen—concomitant administration with chlorzoxazone, analysis in human plasma and urine, effect on pharmacokinetics


Chlorzoxazone (5-chloro-2(3*H*)-benzoxazolone) (I) is a potent skeletal muscle relaxant that is effective in the treatment of skeletal muscle spasms. Onset of therapeutic activity is observed within 1 hr, with a duration usually up to 6 hr (1). Chlorzoxazone exhibits minimal adverse effects and almost no GI irritation.

The data and results presented in this report are part of a study that was performed with 23 normal male subjects to determine the bioavailability of acetaminophen and chlorzoxazone from a commercial combination tablet formulation and an oral suspension. While there exists sufficient information in the literature regarding acetaminophen elimination kinetics (2–6), little has been reported on the disposition characteristics of chlorzoxazone in humans. This report deals primarily with the plasma levels and urinary excretion of chlorzoxazone following administration of a suspension of chlorzoxazone and acetaminophen.

In studies dealing with the metabolic fate of chlorzoxazone in humans, Conney and Burns (7) reported that <1% of the drug was excreted unchanged in urine. Chlorzoxazone was rapidly metabolized in humans to 6-hydroxy-


*0022-3549/83/0900-0991$01.00/0*