(2) S. J. Desai, A. P. Simonelli, and W. I. Higuchi, *ibid.*, **54,** 1459(1965).
(3) S. J. Desai, P. Singh, A. P. Simonelli, and W. I. Higuchi, *ibid.*, **55,** 1224(1966).
(4) *Ibid.*, **55,** 1230(1966).
(5) *Ibid.*, **55,** 1235(1966).
(6) P. Singh, S. J. Desai, A. P. Simonelli, and W. I. Higuchi, *J. Pharm. Sci.*, **56,** 1542(1967).
(7) *Ibid.*, **56,** 1548(1967).
(8) C. L. Levesque, U. S. pat. 2,987,445 (1961).
(9) C. J. Endicott, U. S. pat. 3,087,860 (1963).

ACKNOWLEDGMENTS AND ADDRESSES

Received April 27, 1970, from the *Pharmaceutical Products Division, Abbott Laboratories, North Chicago, IL 60064*

Accepted for publication August 17, 1970.

Presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Washington, D. C. meeting, April 1970.

Drug Release from Methyl Acrylate–Methyl Methacrylate Copolymer Matrix II: Control of Release Rate by Exposure to Acetone Vapor

B. FARHADIEH, S. BORODKIN, and J. D. BUDDENHAGEN

Abstract □ The rate of drug release from tablets made with a methyl acrylate–methyl methacrylate copolymer matrix containing dispersed solid drug can be decreased by exposure to acetone vapor. As in the case of untreated tablets, the quantity of drug released per unit surface area is proportional to the square root of time. An apparatus was developed to study the treatment variables. The extent of reduction in release rate is dependent on the amount of acetone absorbed. This reduction is primarily due to an increase in the tortuosity of the matrix. Generally, the release-rate constant is lowered by decreasing the temperature or increasing the acetone vapor pressure. Thus, exposure of tablets to acetone vapor under controlled conditions is an added means for regulating the drug-release rate.

Keyphrases □ Drug release—methyl acrylate–methyl methacrylate matrix □ Acetone vapor effect—drug release rates, copolymer matrix □ Temperature, pressure effects—acetone absorption, copolymer matrix □ Tortuosity, copolymer matrix—drug release-rate relationship

In the first paper of this series (1), it was shown that the release of drug from a methyl acrylate–methyl methacrylate copolymer matrix follows the relationship proposed by Higuchi (2), in which the amount of drug released per unit surface area is linear with the square root of time. Desai *et al.* (3–6) studied this theoretical relationship extensively, using polyethylene and polyvinyl chloride as plastic matrixes. Endicott (7) demonstrated that the release of drug from tablets compressed with methyl acrylate–methyl methacrylate copolymer can be prolonged by exposure to acetone vapor.

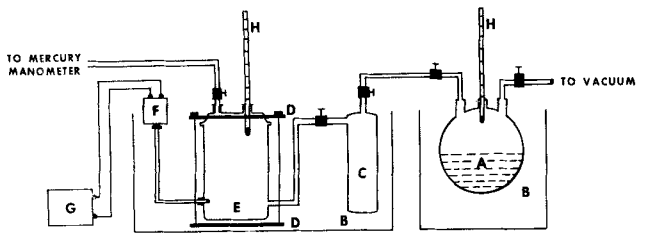

Figure 1—*Acetone vapor treatment apparatus. Key: A, acetone reservoir; B, constant-temperature water bath; C, acetone vapor trap; D, holder plastic plate; E, acetone treatment chamber; F, pressure sensor; G, amplifier and recorder; and H, thermometer.*

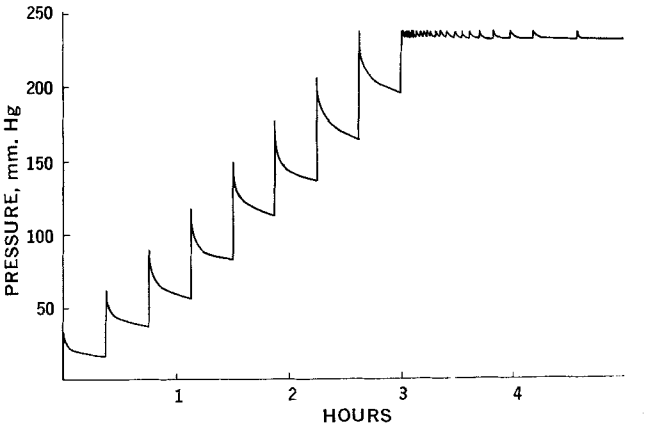

Figure 2—*Recorder tracing of acetone vapor pressure* versus *time at 29°.*

The purposes of this study were: (*a*) to determine whether drug release from tablets treated with acetone vapor would continue to follow the square root of time relationship, and (*b*) to use this relationship to evaluate the effect of different exposure conditions. The tablets used were primarily those made with sodium pentobarbital, although other drugs were examined. The principal acetone exposure variables were temperature and acetone vapor pressure.

EXPERIMENTAL

Chemicals—The plastic used in all tablets was a powdered methyl acrylate–methyl methacrylate copolymer (8).[1] This polymer is insoluble and inert in aqueous media at all pH values. The acetone was reagent grade. All drugs were USP or NF. The densities, diffusion constants, solubilities, and particle-size ranges of these drugs were determined previously (1).

Tablet Compression—All tablets were compressed on a Manesty

[1] Rohm & Haas Co., Philadelphia, Pa.

Table I—Effect of Acetone Vapor Exposure on Release Rate of Drug from Tablets Treated at 28°

Drug	Concentration, mg./Tablet	Acetone Vapor Pressure, mm. Hg	Acetone Absorbed, mg./Tablet	ϵ	τ	$k \times 10^4$, g. cm.$^{-2}$ sec.$^{-1/2}$	$t_{1/2}$, hr.
Sodium pentobarbital	100	Untreated	0	0.575	9.24	5.38	3.38
Sodium pentobarbital	100	244	36.2	0.538	82.2	1.96	25.4
Methapyrilene HCl	100	Untreated	0	0.487	12.2	5.48	3.25
Methapyrilene HCl	100	227	18.1	0.463	37.7	3.08	10.3
Ephedrine HCl	50	Untreated	0	0.375	36.2	1.46	11.5
Ephedrine HCl	50	170	17.1	0.388	46.7	1.28	14.9
Dextromethorphan HBr	30	Untreated	0	0.376	14.2	0.606	23.9
Dextromethorphan HBr	30	172	19.4	0.367	57.6	0.299	98.4

layer press equipped with 1.04-cm. ($^{13}/_{32}$-in.) flat surface punches and dies. Except where stated, tablets used weighed 242 mg. and had an average hardness of 12.0 Strong-Cobb units.

Acetone Vapor Treatment Apparatus—The basic apparatus used consists of an acetone vapor generator, a trap, a treatment chamber, a pressure-sensing device, and a recorder (Fig. 1). The acetone vapor generator consists of a round-bottom, three-necked flask equipped with a thermometer, a stopcock to a vacuum line, and a second stopcock leading to the treatment chamber. The acetone vapor is generated by placing 200 ml. of acetone in the flask, submerging it into a constant-temperature bath maintained about 6° above the treatment temperature, and flushing the air from the flask by drawing a vacuum several times. The acetone vapor is then introduced through the trap into the treatment chamber, both immersed in a constant-temperature bath. The treatment chamber is a resin kettle flask with a removable top and has openings for a thermometer, a mercury manometer, a stopcock to the trap, and connection to the pressure sensor. This sensor, a Statham[2] temperature-compensated absolute pressure transducer, is immersed in the constant-temperature bath and connected through an Ellis[3] bridge amplifier to a model SR Sargent[4] recorder.

Acetone Treatment Procedure—The sensor response is calibrated into pressure from 0–500 mm. Hg, at the temperature of the run by introducing increments of air into the totally evacuated treatment chamber and reading the pressure on the mercury manometer. The treatment chamber is removed from the bath and opened, and 22.0 ± 0.1 g. of tablets is introduced. The chamber is then returned to the bath without the connection to the mercury manometer, and the system is evacuated with a vacuum pump. Acetone vapor is introduced slowly in increments until the desired vapor pressure is attained. Additional portions of acetone are then injected to maintain the vapor pressure within 3 mm. Hg of the desired level. These injections are continued until the rate of acetone absorption by the tablets becomes negligible. At the end of the run the tablets are removed from the treatment chamber, and the acetone is removed from the tablets by evaporation.

Release-Rate Studies—All release-rate studies were on a single surface, using the method described in the first paper of this series (1).

RESULTS AND DISCUSSION

Acetone Absorption—Figure 2 shows a typical recorder tracing of acetone vapor pressure *versus* time. The pressure decreases observed at each interval were due to acetone absorption by the tablets. That these truly reflected tablet absorption was demonstrated by observing no pressure changes in a run in which the tablets were omitted. The amount of acetone absorbed by the tablets at each increment was calculated from the recorded pressure drop. By assuming ideality, the pressure decrease was converted to milligrams of acetone absorbed per tablet from the following equation:

$$W = \frac{1000\,PVM}{760\,RTN} \qquad \text{(Eq. 1)}$$

where W = milligrams acetone absorbed per tablet, P = vapor pressure decrease expressed in mm. Hg, V = volume of treatment chamber (1.46 l.), M = molecular weight (58.08), R = gas law constant (0.082 l. atm. deg.$^{-1}$ mole^{-1}), T = absolute temperature, and N = number of tablets.

The amount of acetone absorbed was dependent on the conditions used. In the cases studied, this varied from 16 to 45 mg./tablet. Weight loss studies with a Cahn Electrobalance[5] on tablets immediately after completion of treatment confirmed the accuracy of the acetone weight absorption.

Drug-Release Rate—Except for very mild conditions, exposure to acetone vapor was found to decrease the drug-release rate from the

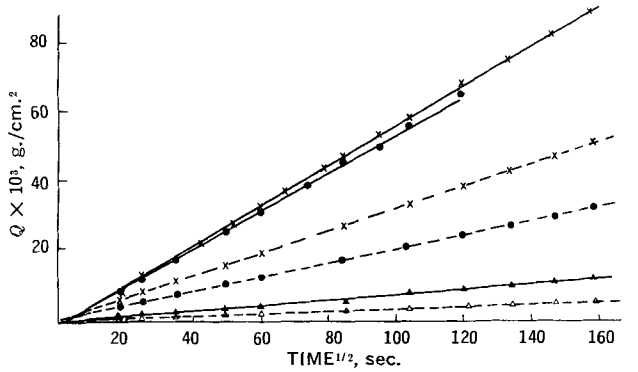

Figure 3—*Comparison of release rates between acetone vapor-treated and untreated tablets. Key: -x—x-, sodium pentobarbital untreated; -●—●-, methapyrilene HCl untreated; -▲—▲-, dextromethorphan HBr untreated; -x- - -x-, sodium pentobarbital treated; -●- - -●-, methapyrilene HCl treated; and -△- - -△-, dextromethorphan HBr treated.*

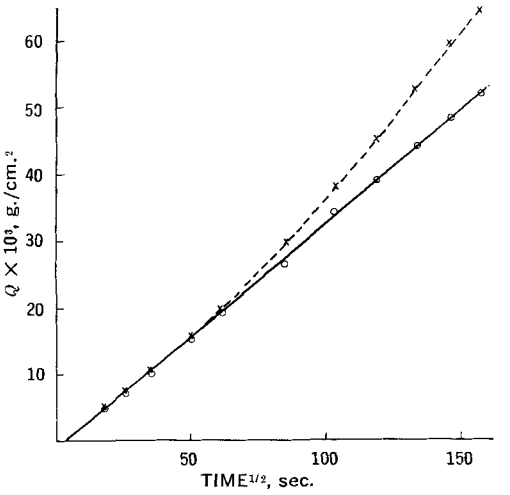

Figure 4—*Effect of hardness on the release of sodium pentobarbital from tablets treated at 30° and 240 mm. Hg. Key: ×, hardness > 27; and ○, hardness = 13.0.*

[2] Statham Instruments, Inc., Los Angeles, Calif.
[3] Ellis Associates, Pelham, N. Y.
[4] E. H. Sargent and Co., Chicago, Ill.
[5] Cahn Instrument Co., Paramount, Calif.

Table II—Effect of Temperature in the Acetone Vapor Treatment of 100-mg. Sodium Pentobarbital Tablets at Two Different Vapor Pressures

Acetone Vapor Pressure, mm. Hg	Temperature	Acetone Absorbed, mg./Tablet	ϵ	τ	$k \times 10^4$, g. cm.$^{-2}$ sec.$^{-1/2}$	$t_{1/2}$, hr.
Untreated tablets		0	0.575	9.24	5.38	3.38
217	25°	33.9	0.516	195.4	1.27	60.6
217	28°	31.1	0.536	50.6	2.48	15.9
217	31°	26.1	0.551	18.6	4.01	6.08
217	34°	18.4	0.560	12.2	4.79	4.26
217	37°	16.2	0.567	11.5	4.93	4.02
244	28°	36.2	0.538	82.2	1.96	25.4
244	31°	29.3	0.540	36.4	2.91	11.5
244	34°	22.5	0.551	16.6	4.19	5.57
244	37°	19.0	0.559	13.3	4.64	4.54

tablets. As with untreated tablets, drug release continued to follow Higuchi's (2) theoretical relationship:

$$Q = \left[\frac{D\epsilon}{\tau}(2A - \epsilon C_S)C_S t\right]^{1/2} \qquad \text{(Eq. 2)}$$

where Q = amount of drug released after time t per unit exposed area, D = diffusivity of the drug in the permeating fluid, τ = tortuosity, A = amount of drug present in the matrix per unit volume, C_S = solubility of the drug in the permeating fluid, and ϵ = porosity of the matrix. This was found to be the case with all drugs tested. Plots of Q *versus* $t^{1/2}$ for both acetone-exposed and untreated tablets are shown in Fig. 3. The graph demonstrates both the continued linearity and the reduced release rate resulting from acetone vapor treatment.

The calculated values for porosity, tortuosity, release-rate constant, and half-life for both acetone-treated and untreated tablets are compared in Table I. The method of calculation was previously described (1). It is apparent from an examination of the data that reduction in the release-rate constant is primarily due to increased tortuosity of the matrix.

As in the case of untreated tablets, the release-rate constants after acetone treatment did not show significant change with hardness. However, when sodium pentobarbital tablets with hardness greater than 22 Strong-Cobb units were treated, deviation from linearity was observed. This deviation increased with hardness. Figure 4 compares the release rates from tablets with hardnesses of 13 and 27 treated under the same conditions. Although the initial rates were identical, the release from the harder tablet soon began to approach that of untreated tablets. Apparently, with high hardnesses, acetone vapor

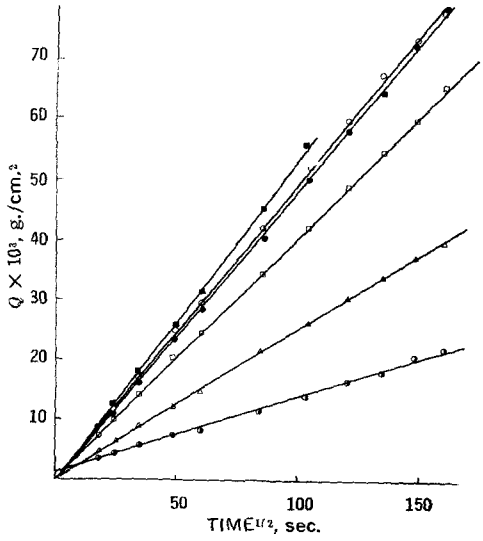

Figure 5—*Effect of temperature on the release rate from 100-mg. sodium pentobarbital tablets at 217 mm. Hg. Key:* ■, *untreated;* ○, *37°;* ●, *34°;* □, *31°;* △, *28°; and* ◑, *25°.*

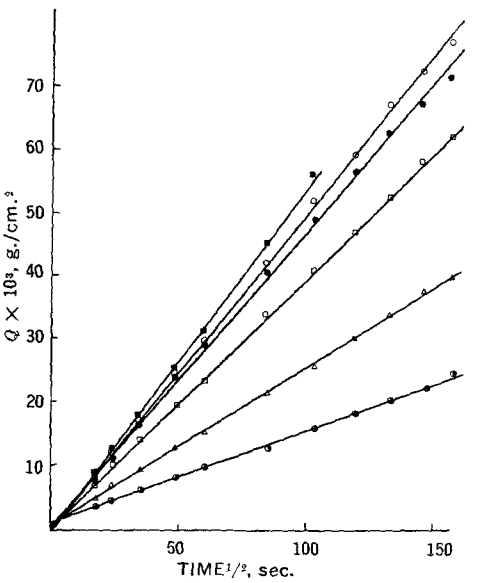

Figure 6—*Effect of acetone vapor pressure on the release rate from 100-mg. sodium pentobarbital tablets treated at 37°. Key:* ■, *untreated;* ○, *217 mm. Hg;* ●, *244 mm. Hg;* □, *267 mm. Hg;* △, *307 mm. Hg; and* ◑, *347 mm. Hg.*

penetration is reduced, resulting in a decrease in tortuosity with increasing distance from the tablet surface.

Effect of Treatment Temperature and Pressure—A series of 15 experiments was run with sodium pentobarbital tablets to study the effects of treatment temperature and acetone vapor pressure on the drug release rate.

Figure 5 and Table II summarize the effects of treatment temperature. The data show that reducing the temperature increases the acetone absorption and lowers the release-rate constant. The maximum rate reduction was achieved when condensation temperature was approached. Table II shows that rate reduction can be attributed primarily to increased matrix tortuosity. However, a decrease in porosity accompanies the treatment temperature decrease.

The effects of acetone vapor pressure on sodium pentobarbital tablets at three temperatures are summarized in Table III. Figure 6 shows the slopes obtained at 37°. The results demonstrate that increasing the acetone vapor pressure increases the acetone absorption and reduces the release-rate constant. As in the case of temperature, the maximum reduction is obtained as condensation pressure is approached. Again, higher tortuosity and lower porosity accompany the increased vapor pressure, with the tortuosity having the major effect on drug release.

An analysis of the data reveals that the extent of release-rate reduction by temperature and pressure effects is governed solely by how far away the selected treatment is from condensation condi-

Table III—Effect of Acetone Vapor Pressure on the Release Rate of Drug from 100-mg. Sodium Pentobarbital Tablets at Three Different Temperatures

Temperature	Acetone Vapor Pressure, mm. Hg	Acetone Absorbed, mg./Tablet	ϵ	τ	$k \times 10^4$, g. cm.$^{-2}$ sec.$^{-1/2}$	$t_{1/2}$, hr.
Untreated tablets		0	0.575	9.24	5.38	3.38
37°	217	16.2	0.567	11.5	4.93	4.02
37°	244	19.0	0.559	13.3	4.64	4.54
37°	267	25.3	0.559	19.7	3.87	6.52
37°	307	30.7	0.535	52.2	2.44	16.4
37°	347	44.9	0.530	154.9	1.43	47.8
34°	217	18.4	0.560	12.2	4.79	4.26
34°	244	22.5	0.551	16.6	4.19	5.57
34°	267	27.9	0.539	43.2	2.67	13.7
34°	307	39.7	0.534	198.2	1.26	61.5
31°	217	26.1	0.551	18.6	4.01	6.08
31°	244	29.3	0.540	36.4	2.91	11.5
31°	267	32.8	0.528	86.2	1.93	26.2

tions. Thus, the desired reduction of k could be achieved at any temperature by adjusting the appropriate acetone vapor pressure. Conversely, at any vapor pressure the optimum release rate could be attained by manipulation of the treatment temperature. The extent of rate reduction would be limited only by condensation.

SUMMARY AND CONCLUSIONS

An apparatus was developed to study the variables involved in the acetone vapor treatment of tablets made from a methyl acrylate–methyl methacrylate copolymer matrix containing dispersed solid drug. This apparatus allows close control of temperature and acetone vapor pressure. It also allows monitoring of the amount of acetone absorbed throughout the run.

Release from the acetone-treated tablets followed the Higuchi relationship in which the quantity of drug released per unit surface area was proportional to the square root of time. Except under very mild conditions, the drug release rate was reduced. The extent of reduction was related to the amount of acetone absorbed. Generally, increasing the vapor pressure or decreasing the treatment temperature increased acetone absorption. Thus, by manipulation and control of these two variables, the drug release rate may be regulated in a reproducible fashion. The decrease in release rate can be explained primarily on the basis of an increase in matrix tortuosity.

REFERENCES

(1) B. Farhadieh, S. Borodkin, and J. D. Buddenhagen, *J. Pharm. Sci.*, **60**, 209(1971).

(2) T. Higuchi, *ibid.*, **52**, 1145(1963).

(3) S. J. Desai, A. P. Simonelli, and W. I. Higuchi, *ibid.*, **54**, 1459 (1965).

(4) S. J. Desai, P. Singh, A. P. Simonelli, and W. I. Higuchi, *ibid.*, **55**, 1224(1966).

(5) *Ibid.*, **55**, 1230 (1966).

(6) *Ibid.*, **55**, 1235(1966).

(7) C. J. Endicott, U. S. pat. 3,087,860 (1963).

(8) C. L. Levesque, U. S. pat. 2,987,445 (1961).

ACKNOWLEDGMENTS AND ADDRESSES

Received April 27, 1970, from the *Pharmaceutical Products Division, Abbott Laboratories, North Chicago, IL 60064*

Accepted for publication August 17, 1970.

Presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Washington, D. C. meeting, April 1970.

Drug Biotransformation Interactions in Man III: Acetaminophen and Salicylamide

GERHARD LEVY and HIDEO YAMADA*

Abstract □ Acetaminophen (1 and 2 g.), salicylamide (1 g.), and 1 g. acetaminophen followed 1.5 hr. later by 1 or 2 g. salicylamide were administered in aqueous solutions to healthy human subjects. Urine was collected every 15–30 min. for the first 4–5 hr. and then at longer intervals. The urine samples were analyzed for acetaminophen, acetaminophen sulfate, acetaminophen glucuronide, salicylamide, salicylamide sulfate, and salicylamide glucuronide. The excretion rates of acetaminophen sulfate and acetaminophen glucuronide decreased immediately after administration of salicylamide. Acetaminophen decreased the formation of salicylamide sulfate. Coadministration of L-cysteine (a source of sulfate) prevented this effect and also increased the excretion of acetaminophen sulfate. The results indicate a competitive inhibition in the formation of acetaminophen sulfate and salicylamide sulfate and suggest also a competitive inhibition in the formation of acetaminophen glucuronide and salicylamide glucuronide.

Keyphrases □ Acetaminophen, salicylamide—biotransformation interaction, human □ Biotransformation interaction—acetaminophen, salicylamide □ Metabolites, acetaminophen, salicylamide—isolated, identified □ Colorimetric analysis—spectrophotometer

Previous reports from this laboratory have shown that the formation of salicylamide sulfate from salicylamide is easily saturated in man (1) and that there occurs a mutual inhibition of glucuronide formation by salicylamide and salicylate when these drugs are administered concomitantly (2). Since acetaminophen, like salicylamide, is eliminated primarily by glucuronide and sulfate formation, and since these mild analgesic and antipyretic drugs are often taken together, the effect of each on the biotransformation of the other has been investigated.

EXPERIMENTAL

Healthy, male, ambulatory human subjects received orally 1 or 2 g. acetaminophen in one test, 1 g. salicylamide in the second test, and 1 g. acetaminophen followed 1.5 hr. later by 1 or 2 g. salicylamide in the third test. Intervals between tests were at least 1 week. The drugs were administered in aqueous solution in the morning on an empty stomach. Food was withheld for at least 2 hr. thereafter. Urine was collected every 15–30 min. for the first 4–5 hr. and then at longer intervals for at least 24 hr. About 50 ml. of water was ingested after each urine collection to assure adequate urine output.

Determination of Acetaminophen and Its Metabolites in Urine—Free acetaminophen was extracted from urine by a method similar to that of Brodie and Axelrod (3). Acetaminophen glucuronide and acetaminophen sulfate were hydrolyzed enzymatically and then extracted as acetaminophen. The concentration of this drug was determined by a modification of the colorimetric method of Welch and Conney (4).

Specifically, free acetaminophen was extracted by adding 4 g. sodium chloride and 15 ml. ether[1] to 10 ml. urine. This mixture was shaken mechanically for 15 min. and centrifuged to separate the phases. Ten milliliters of the ether phase was extracted with 3 ml. 0.1 *N* sodium hydroxide solution by shaking 5 min. and centrifuging. One-half milliliter of the aqueous phase was pipeted into a graduated test tube, and 0.5 ml. 4 *N* hydrochloric acid was added. The test tube was then placed in a boiling water bath for 30 min. The solution was then cooled to room temperature, and 10 ml. phenol–hypobromite mixture (4) and sufficient distilled water to yield a total volume of 11 ml. were added. Forty minutes later, the absorbance of the solution at 625 nm. was determined spectrophotometrically. Reagent blank determinations were made by using water instead of urine in the procedure. A urine sample containing 2 mg. acetaminophen/100 ml. will yield a reagent phase with an absorbance of about 0.21/cm. pathlength by this method.

[1] Ether for Anesthesia, Merck, purified by successive washings with 1 *N* NaOH, 1 *N* HCl, and three washings with distilled water.