from 21 to 72 min for the three 250-mg tablets and was >2 hr for all three 500-mg tablets.

Because of the small range in 30% dissolution times and the excessively long 60% dissolution times, only the times for 40 and 50% dissolution were compared to the 24-hr cumulative percent recoveries. The correlation between dissolution time and urinary excretion was poor, although the attempt at correlation may have failed because of the previously cited lack of sink conditions during the dissolution rate determinations. The correlation coefficients, using the times for 40 and 50% dissolution, were only −0.352 and −0.399, respectively.

The disintegration times used for correlation with the urinary excretion data were determined without disks in the disintegration chambers, even though the USP XIX states that disks should be present. The data without disks were utilized because of the small range in disintegration times when the disks were present. In contrast to the correlation between dissolution and urinary excretion at 24 hr, the correlation between disintegration time and urinary excretion was considerably better, with a correlation coefficient of −0.829 ($p = 0.05$). However, the mean disintegration times employed for Products 3 and 6 were somewhat arbitrary because tablets requiring >30 min were averaged in as 30 min.

The results of these studies suggest that the present USP XIX disintegration specification should be revised to omit the use of disks in the apparatus. Moreover, a dissolution rate specification requiring 900 ml of distilled water as the dissolution medium apparently would not be useful in predicting the *in vivo* performance of chlorothiazide tablets.

REFERENCES

(1) *Fed. Regist.*, Jan. 7, 1977, Part III, V. 42, No. 5, 1649.

(2) W. F. Charnicki, F. A. Bacher, S. A. Freeman, and D. H. DeCesare, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 656 (1959).

(3) J. E. Baer, H. L. Leidy, A. V. Brooks, and K. H. Beyer, *J. Pharmacol. Exp. Ther.*, **125**, 295 (1959).

(4) "Product Information Summary-Diuril," Merck Sharp and Dohme, West Point, Pa.

(5) R. E. Kauffman and D. L. Azarnoff, *Clin. Pharmacol. Ther.*, **14**, 886 (1973).

(6) M. C. Meyer and A. B. Straughn, *Curr. Ther. Res.*, **22**, 573 (1977).

(7) H. R. Brettell, J. K. Aikawa, and G. S. Gordon, *Arch. Intern. Med.*, **106**, 57 (1960).

(8) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975, p. 84.

(9) E. J. Williams, *Aust. J. Sci. Res. A*, **2**, 149 (1949).

(10) B. J. Winer, "Statistical Principles in Experimental Design," McGraw-Hill, New York, N.Y., 1971, pp. 185–196.

(11) M. Pernarowski, in "Dissolution Technology," L. J. Leeson and J. T. Carstensen, Eds., Industrial Pharmaceutical Technology Section of the Academy of Pharmaceutical Sciences, Washington, D.C., 1974, pp. 67–70.

(12) M. C. Meyer, A. P. Melikian, P. L. Whyatt, and G. W. A. Slywka, *Curr. Ther. Res.*, **17**, 570 (1975).

(13) D. E. Resetarits and T. R. Bates, "Abstracts," APhA Academy of Pharmaceutical Sciences, Hollywood, Fla., meeting, Nov. 12–16, 1978, p. 82, No. 26.

(14) V. P. Shah, P. Sojka, V. K. Prasad, and B. E. Cabana, "Abstracts," APhA Academy of Pharmaceutical Sciences, Montreal meeting, May 13–18, 1978, p. 195, No. 36.

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Effect of Temperature and an Ion-Exchange Resin on Cation Diffusion through Silicone Polymer Tubing

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Received October 23, 1978, from the *Department of Pharmaceutics, College of Pharmacy, University of Utah, Salt Lake City, UT 84112.* Accepted for publication February 28, 1979.

Abstract □ Permeation of cations through silicone rubber tubing was measured, and the effect of an ion-exchange resin on the cation diffusion was determined. Silicone rubber has been used as a biomedical polymer and shows a very low solubility to ionizable species. Correlations between the calculated diffusion coefficients, with and without the resin, depended on the charge and number of waters of hydration for each cation. These increases ranged from 1.11 for potassium to 3.06 for iron, multiplied by the diffusion coefficient as a result of the resin. Solubilities of each cation in the polymer were temperature dependent. Activation energies were calculated for each cation by measuring the increased permeation with increasing temperature, with and without the resin. Decreasing magnitudes of activation energies ranged from 0.91 for sodium to 0.57 for iron when the resin was present. Correlations were established between the measured activation energies and reported free energy change for the hydration of each cation.

Keyphrases □ Cations—diffusion through silicone polymer tubing, effect of temperature and ion-exchange resin □ Temperature—effect on cation diffusion through silicone polymer tubing □ Ion-exchange resins—effect on cation diffusion through silicone polymer tubing □ Dosage forms, sustained release—silicone polymer tubing, effect of temperature and ion-exchange resin on cation diffusion

Because of the minimal body tissue response and relatively high diffusivities of hydrophobic solutes, polydimethylsilicone is an excellent candidate for sustained-release medication implantation devices. Hydrophobic solute diffusion through this polymer is well documented (1–6), showing high rates of diffusivity and polymer solubility.

BACKGROUND

Little information is available on the permeation of charged or uncharged solutes that show a low solubility in silicone films. In evaluating the function of silicone heart valves, a previous investigator (7) reported that hydrophobic dyes such as rhodamine diffused into the valve, while hydrophilic dyes such as methylene blue did not. Silicone capsules containing normal saline, 5% dextrose in water, sodium citrate, and a calcium-saturated solution of edetic acid showed a lack of permeation of these solutes through the polymer (8).

Permeation of both charged and uncharged solutes through silicone membranes has been measured (9). Silicone was not permeated by the charged organic molecules but was permeated by the uncharged organic molecules, which were lipophilic. Both atropine base and histamine diffused through silicone rubber tubes (10). Histamine is water soluble.

The limited permeability of charged or water-soluble solutes has re-

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stricted the use of silicone as a potential drug delivery carrier for water-soluble or charged drugs. If an additional factor could be added to enhance the permeation of charged solutes through silicone rubber, new delivery systems could be devised for these drugs.

The use of charged nondiffusable polyelectrolytes to increase coion diffusion was suggested previously (11). Carboxymethylcellulose sodium greatly increased the diffusion of both penicillin and salicylate ions, more than doubling the observed transport rate and equilibrium distribution compared to the rate and distribution when the resin was not present. Similar results were obtained by investigators (12) who measured electrostatic forces between polyelectrolyte solutions and counterions and the effect of these forces on counterion diffusion. It has been observed in this laboratory (13) that a positively charged polyelectrolyte increases the diffusion rate and equilibrium concentrations of cations by its presence, based on the Donnan membrane effect.

The purpose of the work was to determine the effects of an anion-exchange resin on the diffusion rate of the cations through silicone polymer. It was postulated that the resin would provide an additional driving force due to electrostatic repulsion between the resin and the cations and would increase their diffusion rate.

EXPERIMENTAL

Materials—The diffusion species used were the chloride salts of potassium, sodium, calcium, and iron prepared from reagent grade chemicals. Silicone[1] polymer tubing and medical grade adhesive[2] were used throughout the experiment. The tubing sizes (inside diameter by outside diameter in centimeters) were: A, 0.335 × 0.465; B, 0.267 × 0.318; and C, 0.292 × 0.318. The anion-exchange resin[3] was a trimethylbenzylammonium chloride polymer. Deionized water was used in the preparation of all solutions.

Methods—Specific lengths of silicone polymer tubing were sealed at one end with the adhesive and allowed to cure. The tubes were filled with aqueous solutions of 1-mg/ml concentrations of each cation, leaving a small air space at the top of each tube, and then were sealed with the adhesive. Two tubes were prepared for each cation, one containing only the cation solution and the other containing the cation solution plus 10 mg of the resin/ml.

The filled polymer tubes were placed in glass tubes, and a deionized water receptor phase was added in a volume sufficient to immerse completely the polymer tube and leave only a small air space after the glass tube was stoppered. The prepared glass tubes were rotated end over end at a constant 16 rpm, which caused the air bubbles in the silicone tubes to traverse the entire length of the tube during each half-revolution. This procedure produced a uniform distribution of the resin and a continual solution mixing within the polymer tubes. This rotation also produced receptor phase mixing.

The receptor phase was changed weekly and analyzed for cation concentration by atomic absorption spectrophotometry[4]. The receptor phase for the 1st week was discarded because 4–6 days was required before any cations appeared in the receptor phase. Temperature regulation was maintained by placing the glass tubes in an incubator; all solutions and equipment were brought to the appropriate temperature before the experiments.

The solubility of each cation in the silicone polymer was determined by using a known polymer volume and measuring the ion depletion from a solution of known concentration and volume. The polymer was placed in each cation solution for 7 days, removed, and desorbed by deionized water for another 7 days. The membrane was used for cation solubility determinations after drying in an evacuated chamber to a constant weight.

RESULTS AND DISCUSSION

The mathematical relationship for the diffusion from a cylinder consists of a membrane diffusional component and a diffusional layer component. Research into the diffusion from polymeric systems (14) indicates that the rate-determining step is the membrane diffusional component and that the diffusion rate follows Fick's law. A modified form of the general case for diffusion through a cylinder, as obtained from the literature (15), is given by:

[1] Silastic, Dow Corning Corp., Midland, Mich.
[2] Silastic Type A, Dow Corning Corp., Midland, Mich.
[3] Dowex-1, Sigma Chemical Corp., St. Louis, Mo.
[4] Model 305-A, Perkin-Elmer Corp., Norwalk, Conn.

Table I—Cation Solubility in Silicone Rubber at Different Temperatures

Temperature	Potassium, $\mu g/cm^3$	Sodium, $\mu g/cm^3$	Calcium, $\mu g/cm^3$	Iron (Ferric), $\mu g/cm^3$
15°	1.44	1.37	1.38	1.20
25°	1.72	1.64	1.66	1.45
35°	1.98	1.96	1.98	1.74

$$J = 2\pi h D_m C_m / \ln\left(\frac{\text{o.d.}}{\text{i.d.}}\right) \qquad \text{(Eq. 1)}$$

where J is the flux, h is the cylinder length, D_m is the diffusion coefficient, C_m is the solubility of the diffusing species in the polymer, and o.d. and i.d. are the outer and inner wall diameters, respectively. Flux was determined by measuring the concentration of each ion as it appears in the receptor phase and calculating the cumulative release (micrograms) per centimeter of tube length over the measured time periods.

The relation of activation energies to the diffusion coefficients are shown by Eq. 2, a modified Arrhenius equation:

$$\ln\frac{D_2}{D_1} = \frac{E_a}{R}\frac{(T_2 - T_1)}{T_2 T_1} \qquad \text{(Eq. 2)}$$

where D_1 is the diffusion coefficient at temperature T_1, D_2 is the diffusion coefficient at temperature T_2, E_a is the activation energy, and R is the gas content; E_a was calculated from the slope of ln D *versus* $(1/t)$.

The filler used in silicone polymer reportedly (16–18) is high surface area fumed silica, which physically adsorbs many diffusing species. This adsorption may physically remove such species from the diffusion process or slow down the diffusion rate. Therefore, these adsorption sites would influence species solubility and diffusion lag times for each ion. This factor was the primary reason for presoaking the polymer in a solution of each ion before polymer solubilities were determined.

The solubilities of the four cations in silicone rubber are shown in Table I. Iron had the least solubility, sodium and calcium solubilities were nearly identical, and potassium showed the greatest solubility. The solubilities of all ions increased with temperature.

A typical concentration *versus* time plot is shown in Fig. 1. A cumulative total of micrograms of calcium that diffused through the silicone tubes, with and without the resin at 25°, is plotted against time. The effects of the resin are visible, as can be seen from the increasing slopes of the lines. The linearity of the plotted data is reasonable due to the differences in ion concentrations on each side of the polymer. Few ions

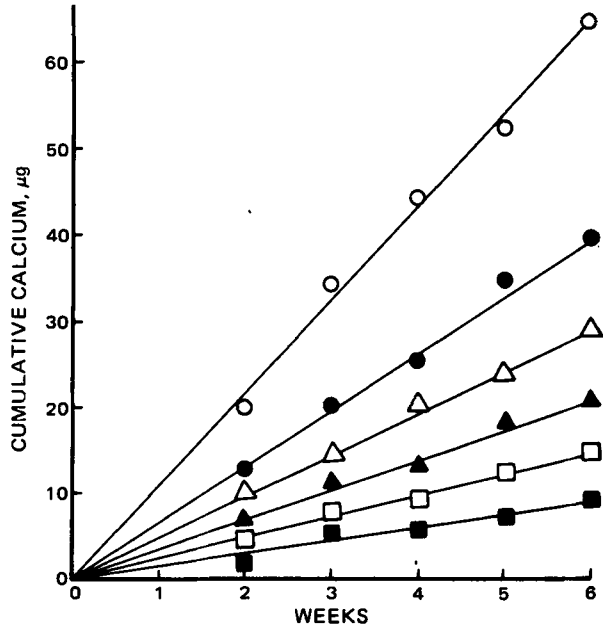

Figure 1—*Cumulative micrograms of calcium* versus *time at 25°. Key:* ○, *calcium plus resin for Tube C;* ●, *calcium for Tube C;* △, *calcium plus resin for Tube B;* ▲, *calcium for Tube B;* □, *calcium plus resin for Tube A; and* ■, *calcium for Tube A.*

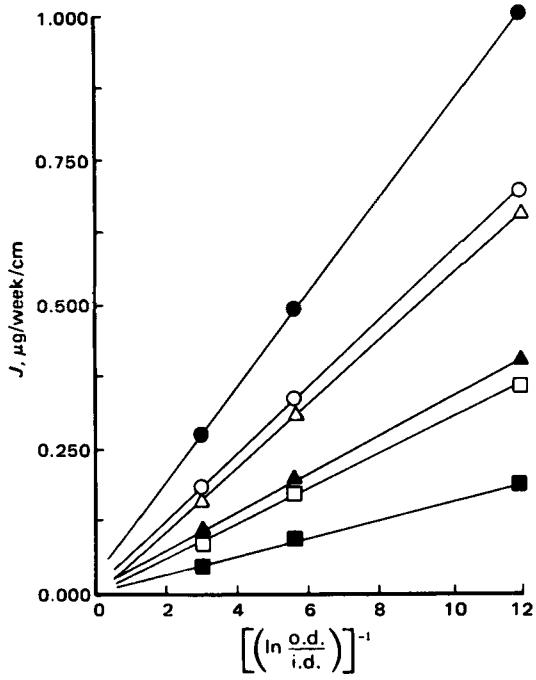

Figure 2—*Flux (J) for calcium permeation from Silastic polymer tubes versus [ln (o.d./i.d.)]$^{-1}$ for Tubes A–C. Key: ●, calcium plus resin at 35°; ○, calcium at 35°; △, calcium plus resin at 25°; ▲, calcium at 25°; □, calcium plus resin at 15°; and ■, calcium at 15°.*

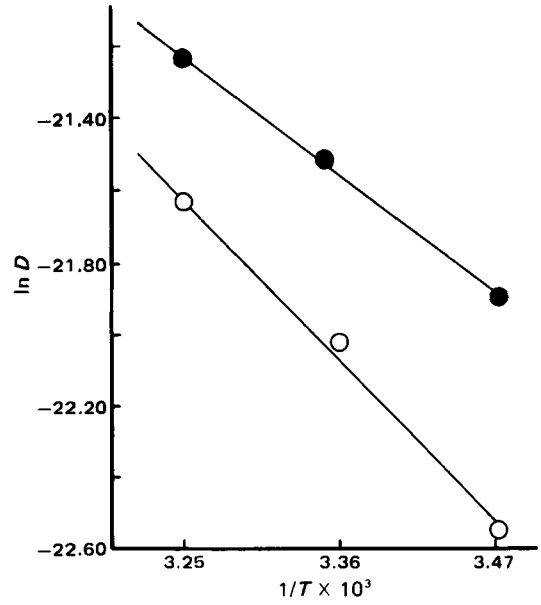

Figure 3—*Arrhenius plot of ln* D versus *1/*T *for calcium (○) and calcium plus resin (●).*

permeated the tubing relative to the ionic concentration within the tube, the latter being almost constant.

The diffusion results are shown in Fig. 2 for calcium, where the flux, J, is plotted against [ln (o.d./i.d.)]$^{-1}$ of each silicone tube. This figure depicts the data from the measured flux at three temperatures, with and without the resin. The effect of the resin on its diffusion through the polymer is in the order: iron > calcium > sodium > potassium.

Diffusion coefficients calculated from the slopes of these plots are given in Table II. Here D_m is the diffusion coefficient where no resin was present, and D_m^* is the diffusion coefficient where the resin was present. The correlation coefficients were greater than 0.99.

A comparison of D_m *versus* D_m^* was obtained from the ratio D_m^*/D_m at 25°: potassium, 1.11; sodium, 1.26; calcium, 1.62; and iron, 1.81. Because the increase in the diffusion rate due to the resin is based on the repulsion of like charges on the resin and the ions, for a given equal weight concentration the charge groups per unit volume for the ions is in the order: iron > calcium > sodium > potassium.

The calculated effect the resin would have on the increased diffusion rate for these ions using the Donnan equilibrium, times the diffusion where no resin was present, is: potassium, 1.46; sodium, 2.48; calcium, 2.85; and iron, 3.06. These figures were obtained by calculating the gram equivalent per liter of each cation present in a 1-mg/ml concentration and the electrical repulsion due to the resin in a 10-mg/ml concentration. Comparison of the calculated to actual increased diffusion rate caused by the resin demonstrates that the actual rate was less than the calculated rate. This finding could be due, in part, to the limited solubility of the ions in the polymer, which may be the rate-limiting step for the diffusion process.

Activation energies as calculated from the slopes of the lines of plots similar to Fig. 3 are given in Table III. Figure 3 is a plot of ln D *versus* $1/T$ for calcium. Decreased activation energies can be seen by the difference of the slopes for the resin and nonresin plots; E_a signifies that no resin was present, and E_a^* indicates that the resin was present in the silicone tube. Correlation coefficients all exceeded 0.99.

Activation energies decreased due to the resin in the same order and about to the same extent as the diffusion coefficients increased. Ratios of E_a^*/E_a are: potassium, 0.91; sodium, 0.81; calcium, 0.72; and iron, 0.57.

Table IV is a comparison of activation energy and various parameters obtained from the literature. In each case, the activation energy where no resin was present, as calculated from the results of this experiment, was only slightly larger than the free energy change for the ion hydration.

These data may suggest that the ions utilize dehydration energy for the initial movement into the membrane. Because of the hydrophobic nature of silicone rubber, the measured activation energies may be important in the hypothesis that only the dehydrated ion permeates these types of polymers. When the resin was present, the measured activation energies of the ions for diffusion were less than when no resin was present. The magnitude of decreased activation energies increased as the charge on the ion increased. This effect was due to the increased electrical re-

Table II—Measured Cation Diffusion Coefficients through Silicone Rubber

Cation	Temperature	$D_m \times 10^{10}$, cm^2/sec	$D_m^* \times 10^{10}$, cm^2/sec
Potassium	35°	4.34	4.61
	25°	3.12	3.46
	15°	1.93	2.21
Sodium	35°	3.71	4.41
	25°	2.62	3.30
	15°	1.58	2.20
Calcium	35°	4.03	5.97
	25°	2.80	4.54
	15°	1.59	3.06
Iron (ferric)	35°	3.70	5.94
	25°	2.44	4.42
	15°	1.17	3.08

Table III—Measured Cation Activation Energies

Cation	E_a, kcal/mole	E_a^*, kcal/mole
Potassium	7.3	6.7
Sodium	7.7	6.2
Calcium	8.4	6.1
Iron (ferric)	10.4	6.0

Table IV—Reported Values of the Radius of the Ions (r) (19), the Number of Waters of Hydration (N) (20), and the Free Energy of Hydration for the Ions (ΔG) (21) and E_a Values from Table III

Parameter	Potassium	Sodium	Calcium	Iron (Ferric)
r, Å	1.38	0.95	0.99	0.64
N	3	4	10	12
ΔG, kcal/mole	7.08	7.45	8.16	—
E_a	7.31	7.68	8.40	10.39

pulsion between the resin and the ion as the net charge difference increased. The resin introduced an additional driving force, which reduced the activation energy required for each ion to permeate the membrane.

REFERENCES

(1) P. J. Dziuk and B. Cook, *Endocrinology*, **78**, 208 (1966).

(2) P. J. Dziuk, B. Cook, G. D. Niswender, C. C. Kaltenbach, and B. B. Doane, *Am. J. Vet. Res.*, **29**, 2415 (1968).

(3) F. A. Kincl, G. Benagiano, and I. Angee, *Steroids*, **11**, 673 (1968).

(4) G. Levy and E. J. Mroszczak, *J. Pharm Sci.*, **57**, 235 (1968).

(5) R. H. Reuning and G. Levy, *ibid.*, **58**, 79 (1969).

(6) K. Sundaram and F. A. Kincl, *Steroids*, **12**, 517 (1968).

(7) D. M. Long, speech given at Naval Medical Research Institute, National Naval Medical Center, Bethesda, Md.

(8) J. Folkman and D. Long, *J. Surg. Res.*, **4**, 139 (1964).

(9) E. R. Garrett and P. B. Chemburkar, *J. Pharm. Sci.*, **57**, 944, 949, 1401 (1968).

(10) P. Bass, *Nature*, **208**, 591 (1965).

(11) T. Higuchi, R. Kuramoto, L. Kennon, T. Flanagan, and A. Polk, *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 646 (1954).

(12) E. Pefferkan and R. Varogui, *Eur. Polym. J.*, **6**, 663 (1970).

(13) D. P. Christy, S. W. Kim, and R. V. Petersen, *J. Pharm. Sci.*, in press.

(14) A. L. Tanquary and R. E. Lacey, in "Advances in Experimental Medicine and Biology," vol. 47, Plenum, New York, N.Y., 1974.

(15) J. Crank, "The Mathematics of Diffusion," Oxford University Press, London, England, 1964.

(16) C. F. Most, *J. Appl. Polym. Sci.*, **14**, 1019 (1970).

(17) W. Higuchi and T. Higuchi, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 598 (1960).

(18) K. F. Finger, A. P. Lemberger, T. Higuchi, L. W. Busse, and D. E. Wurster, *ibid.*, **49**, 569 (1960).

(19) R. Noyes, *J. Am. Chem. Soc.*, **84**, 513 (1962).

(20) J. O'm Bockris, "Modern Electrochemistry," vol. 1, Plenum, New York, N.Y., 1970.

(21) M. Jhon, H. B. Lee, S. W. Kim, and J. Andrade, *J. Korean Chem. Soc.*, **20**, 448 (1976).

Antipyretic Effect of Acetaminophen Suppositories in Rats

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Received October 24, 1978, from the *School of Pharmacy, Oregon State University, Corvallis, OR 97331.* Accepted for publication March 6, 1979.

Abstract □ An animal model used yeast-fevered rats to measure the relative antipyretic effects of different commercially available acetaminophen-containing suppositories. A laboratory-prepared acetaminophen-containing suppository and placebo suppositories also were investigated. Release from the suppositories was measured *in vitro*. All acetaminophen products containing 600 mg of drug elicited significant decreases in the rectal temperature of fever-induced rats.

Keyphrases □ Antipyretic agents—acetaminophen, suppositories, rats □ Acetaminophen—antipyretic effects, suppositories, rats □ Dosage forms, solid—suppositories, acetaminophen, antipyretic effects, rats

The antipyretic effect of acetaminophen is well known. However, formulation factors can influence the rate and extent of acetaminophen bioavailability from rectal dosage forms (1–5). Drug release from suppository vehicles is necessary before absorption can occur. Acetaminophen release from various polyethylene glycol vehicles appears to be related to its solubility in the vehicle, which, in turn, is related to vehicle dielectric properties (1, 2). Different formulations of polyethylene glycol suppositories show fairly wide variation in total urinary acetaminophen excretion due to differences in absorption patterns of the rectally administered acetaminophen (1).

The use of rectal suppositories for systemic acetaminophen administration has been the subject of recent studies in humans. The results from a well-controlled, double-blind study in humans indicated no significant differences in antipyretic effect between acetaminophen administration of a hospital pharmacy-prepared suppository and a commercially available tablet dosage form (4). However, large differences in acetaminophen bioavailability from suppositories prepared in two different hospitals were found when they were compared to a commercial rectal product in a urinary excretion study using human subjects (5). The large differences found in the relative bioavailability, peak excretion rates, and times of peak action between the hospital-manufactured acetaminophen suppositories themselves and the commercially obtained product prompted the investigator to suggest the need for *in vivo* testing of hospital-prepared suppositories (5).

The purpose of this study was to compare *in vivo* the antipyretic effects of five different generic acetaminophen suppository products purchased from different commercial sources with acetaminophen-containing and placebo suppositories prepared in this laboratory. The animal model used was a modified version of a previously reported *in vivo* method for measuring the antipyretic effect of aspirin in rats (6).

EXPERIMENTAL

Reagents and Equipment—Petrolatum[1], polyethylene glycol 1540[2], polyethylene glycol 6000[2], polyethylene glycol 400[2], acetaminophen[3], brewer's yeast[4], and ether[5] were used as supplied.

Acetaminophen suppositories, A–E[6], were obtained from commercial sources.

The equipment used included a rectal thermometer[7], thermistor probe[8], wound clip applier[9], and 9-mm wound clips[10].

[1] Matheson, Coleman and Bell, Norwood, OH 45212.
[2] J. T. Baker Chemical Co., Phillipsburg, NJ 08865.
[3] Lot 7032-LSR-43, S. B. Penick, Lyndhurst, NJ 07071.
[4] E. R. Squibb & Sons, Princeton, NJ 08540.
[5] Mallinckrodt, St. Louis, MO 63147.
[6] Product A, Westward, Inc., Eatontown, NJ 07724; Product B, American Quinine, Hospital Division of Natcon Chemicals, Plainview, NJ 11803; Product C, Consolidated Midland Corp., Brewster, NY 10509; Product D, Reiss Williams Co., Division of G & W Laboratories, Port Reading, NJ 07064; and Product E, Upsher-Smith Laboratories, Minneapolis, MN 55415.
[7] Model 47TD, Yellow Springs Instrument Co., Yellow Springs, Ohio.
[8] Series T2 605, Yellow Springs Instrument Co., Yellow Springs, Ohio.
[9] Model 7630, Clay Adams, Division of Becton, Parsippany, NJ 07054.
[10] Clay Adams, Parsippany, NJ 07054.

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