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THE EFFECT OF SELECTED NONIONIC AND ANIONIC GUM DISPERSIONS ON THE EFFECTIVE DIALYSIS RATE AND URINARY EXCRETION RATE OF SALICYLATE

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Abstract:

Comparably viscous nonionic and anionic gum dispersions were found to vary in their effect on salicylate dialysis through a semipermeable membrane. The urinary recovery rate of unchanged salicylate was affected by the coadministration of gums. Methylcellulose 4000 lowered the rate of excretion whereas sodium carboxymethylcellulose increased the rate.

Introduction

Gums are used as granulating agents in the formulation of tablets and as viscosity enhancers in oral liquid preparations. Earlier investigators have described the effects of such agents on drug dissolution, dialysis and absorption. Thus Higuchi and his

associates (1) reported that sodium carboxymethylcellulose and sodium polyacrylate enhanced the dialysis rate of sodium salicylate and potassium benzylpenicillinate through cellophane. Wurster and Taylor (2) reported that an increase in viscosity will result in a decrease in the rate of dissolution and absorption of a drug molecule. Redman et al. (3) showed that the dialysis rate of radioactive iodide was retarded in the presence of suspending agents. Lamy et al. (4) reported that the viscosity of sodium carboxymethylcellulose solutions accounted for the depressed rate of drug transfer in an in vitro model.

Hewitt and Levy (5) observed that the rate and extent of thiamin and riboflavin absorption were not significantly altered by methylcellulose. Levy and Rao (6) reported that the oral absorption of riboflavin-5'-phosphate was increased significantly if 2% sodium alginate was included in the aqueous solution. Davison et al. (7) demonstrated that 2% methylcellulose delayed the oral absorption of sodium salicylate. Levy and Jusko (8) reported that methylcellulose reduced the absorption of ethanol and salicylic acid in rats.

In this paper is presented: (i) the effect of selected nonionic and anionic gum dispersions on the dialysis rate of salicylate through a cellophane membrane; and (ii) human urinary excretion rates of salicylate after ingestion of aqueous dispersions containing these gums.

Experimental

Materials- The chemicals used were obtained from commercial sources: sodium salicylate (U.S.P.)[1], methylcellulose 400 (Premium Grade)[2] (I), methylcellulose

4000 (Premium Grade)[3] (II), hydroxypropyl methylcellulose (Premium Grade)[4] (III), sodium carboxymethylcellulose (Premium Grade)[5] (IV), carboxymethyl hydroxyethylcellulose[6] (V), hydroxypropylcellulose (Food Grade)[7], (VI), hydroxyethylcellulose[8] (VII), NaCl (Reagent Grade)[9], potassium phosphate, monobasic (Reagent Grade)[9], mercuric chloride (N.F.)[10], hydrochloric acid (Reagent Grade)[9].

Preparation of the 2% (w/v) Gum Dispersions- Aqueous dispersions of methylcellulose (Methocel MC 400 and 4000) were prepared according to the hot method described in the manufacturer's product manual[11]. The aqueous dispersions of the remaining gums were made by dissolving the powder in cold distilled water with the aid of a Waring Blendor[12]. The time and intensity of mixing were kept constant for all solutions prepared. Viscosities were determined with the Brookfield Viscometer (Model LVF)[13], using a No. 3 spindle at 60 r.p.m. The viscosities of all the gum dispersions were 400 cps ± 10% with the exception of Methocel MC 4000 which was 4000 cps ± 10%.

Simulated Gastrointestinal Fluids- Simulated Gastric Fluid (SGF) and Simulated Intestinal Fluid (SIF) were prepared according to U.S.P. XVIII (9). In these studies the enzyme component for each of these solutions was omitted.

Dialysis Procedure- The apparatus consisted of a 250-ml. graduated cylinder which served as an outer vessel and a tubular dialysis membrane[14] 203 mm. long and 19 mm. in diameter. The lower end of the dialyzer bag was sealed by inserting a cylindrical Teflon block, 14 mm. high, inside the dialysis tube. A tight fit was insured by clamping an O ring on the outside.

The upper end of the tubing was attached to a Teflon ring 14 mm. high. This in turn was connected by a piece of wire to the arm of the cam-shaft motor unit of a U.S.P. Disintegration Test Apparatus. A Magni-Whirl Constant Temperature Bath[15] was used to maintain the temperature at 37° ± 1°C. The dialyzing bag was raised and lowered 32 times per minute.

One hundred and fifty ml. of SIF was placed in the 250-ml. cylinder (outside compartment). Five ml. of a gum dispersion containing 340 mg. of sodium salicylate was added to 15 ml. of SGF inside the cellophane bag. Five ml. samples were withdrawn from the outside compartment at specified time intervals. The total volume was kept constant by the addition of 5 ml. of SIF to the outside compartment.

Alternatively 20 ml. of gum dispersion containing 340 mg. of sodium salicylate and sufficient concentrated hydrochloric acid to adjust the pH to 1.2 was placed inside the cellophane bag. Sampling of the outside compartment at specified time intervals was conducted as described above.

The concentration of dialyzed salicylate in the outside compartment was determined by the use of a Coleman Hitachi 124 Double Beam Spectrophotometer[16] at a wavelength of 296.5 nm. To account for the sample that was withdrawn, a cumulative correction was made for the previously removed samples in determining the total amount dissolved by using the formula reported by Wurster and Taylor (10):

$$C_t = C_t \text{ meas. } 5/170 \sum_{s=1}^{n=1} (C_s \text{ meas.})$$

C_t meas. denotes the spectrophotometrically measured concentration, while C_t is the corrected concentration of the n^{th} sampling

expected in the medium if previous samples had not been removed. C_s meas. is the uncorrected concentration of the n-1 previous uncorrected sample readings. Five ml.was the volume of outside compartment fluid withdrawn at specified time intervals and 170 ml.was the total number of milliliters present inside and outside the bag.

Urinary Excretion Studies- Four healthy adults emptied their bladders of urine that was used as a blank and then drank a glass of water. One hour later 340 mg. of sodium salicylate dissolved in 20 ml. of aqueous gum dispersion was taken orally followed by a second glass of water. Breakfast was eaten one hour later. Urine collections were made at 1, 2, 4, 6 and 8 hours. Pooled samples of urine were then taken for the following time intervals: 8-24, 24-36 and 36-48 hours. All urine samples were stored in the refrigerator until the last pooled samples were collected. Unchanged salicylate in the urine was assayed according to the method of Trinder (11).

Results and Discussion

Figure 1 illustrates the effect on salicylate dialysis after the addition of 5 ml of 2% gum dispersion and 340 mg of sodium salicylate to 15 ml of S.G.F. in the cellophane bag. After admixture the gum precipitated and salicylic acid crystallized out of solution. As movement of SIF into the inside compartment proceeded, a rise in pH and viscosity and gradual dissolution of salicylic acid crystals resulted.

All of the gums caused a retardation in salicylate dialysis rate when compared with the control. Unexpectedly methylcellulose 4000 had the least innibitory effect on the rate of dialysis

(Figure 1, Line 8). A possible explanation is that under the conditions of the dialytic procedure, rehydration of the precipitated methylcellulose of much higher molecular weight is less efficient. Such inefficient redispersion of the gum would permit more rapid dialysis of salicylate.

Sodium carboxymethylcellulose was next in order (Figure 1, Line 4). The Donnan Membrane Equilibrium is the most likely explanation for the dialysis rate observed with this anionic gum based on the work of Higuchi (1). It is of interest to point out that another anionic gum is next in order, namely, carboxymethyl hydroxyethylcellulose (Figure 1, Line 5).

Figure 2 illustrates the effect on salicylate dialysis with 20 ml of acidified gum dispersion containing 340 mg of sodium salicylate in the inside compartment and SIF on the outside. This larger volume of gum dispersion was investigated *in vitro* since it was intended that the *in vivo* dose of 340 mg of drug would be contained in 20 ml of gum dispersion.

Here again there was a viscosity drop (400 to 10 cps; 4000 to 30 cps) and crystallization of salicylic acid. As before the gum which retarded the dialysis rate the least was methylcellulose 4000 (Figure 2, Line 3). In addition sodium carboxymethylcellulose ranked second.

Some support for the idea of inefficient rehydration to explain the odd result with methylcellulose 4000 is afforded by the data in Figure 3. In these dialytic studies 20 ml of gum dispersion containing 340 mg of sodium salicylate was placed in the bag and dialyzed against SIF. Under these conditions neither gum nor drug precipitation occurred. The gum which retarded salicylate dialysis the least was sodium carboxymethylcellulose

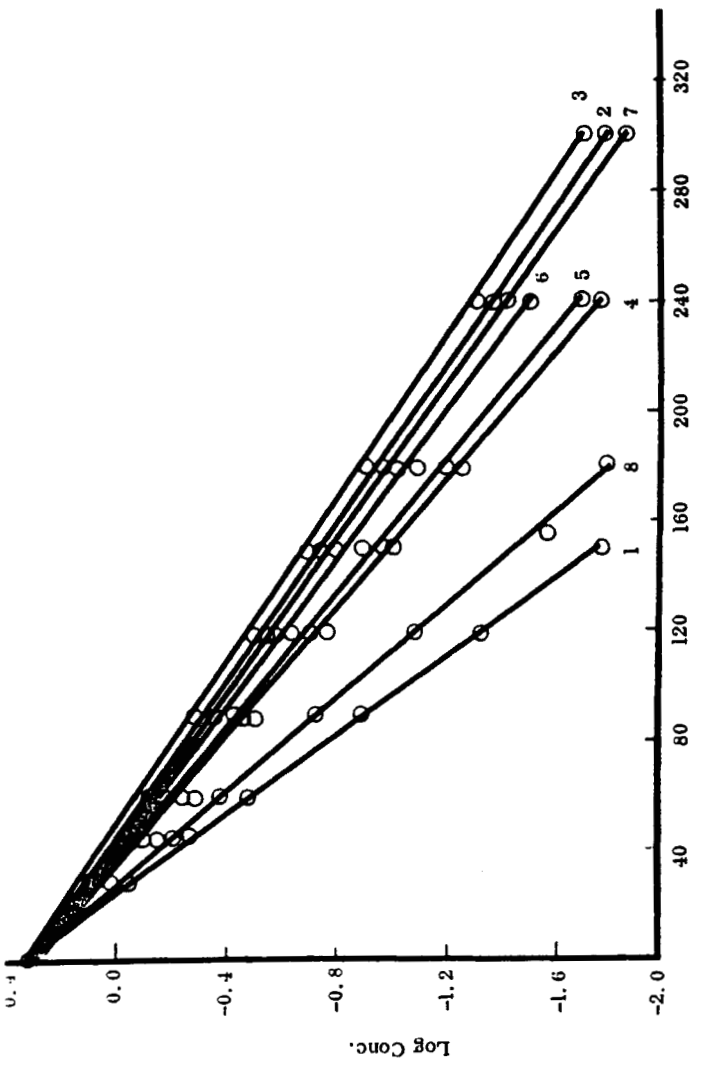

Figure 1. Apparent First Order Profile Effect of Thickening Agents on the Dialysis of Salicylate: SGF/SIF.

Key: 1. Control 2. Klucel F 3. Natrosol 250J
4. Cellulose Gum 7MF 5. CMHEC - 37M
6. Methocel 65 HG 400 7. Methocel HC 400
8. Methocel MC 4000

(Volume of gum solution incorporated: 5 ml.)

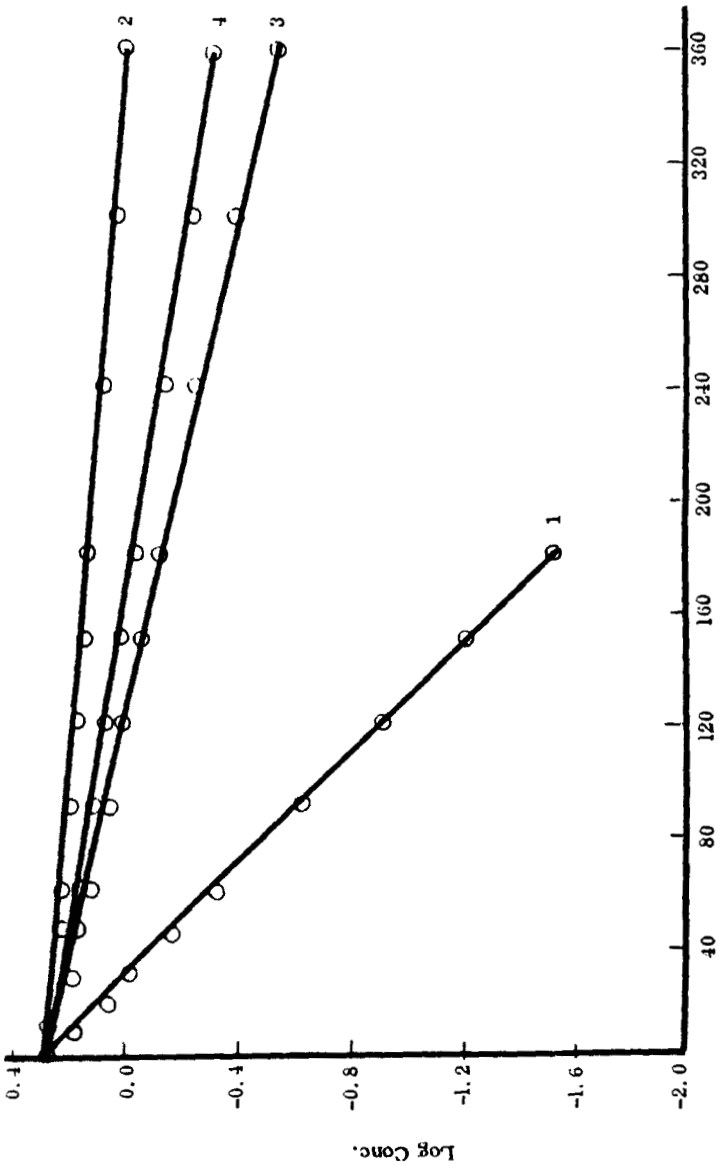

Figure 2. Apparent First Order Profile Effect of Thickening Agents on the Dialysis of Salicylate: SGF/SIF.

Key: 1. Control 2. Methocel MC 400 3. Methocel MC 4000
4. Cellulose Gum 7MF

(Volume of gum solution incorporated: 20 ml)

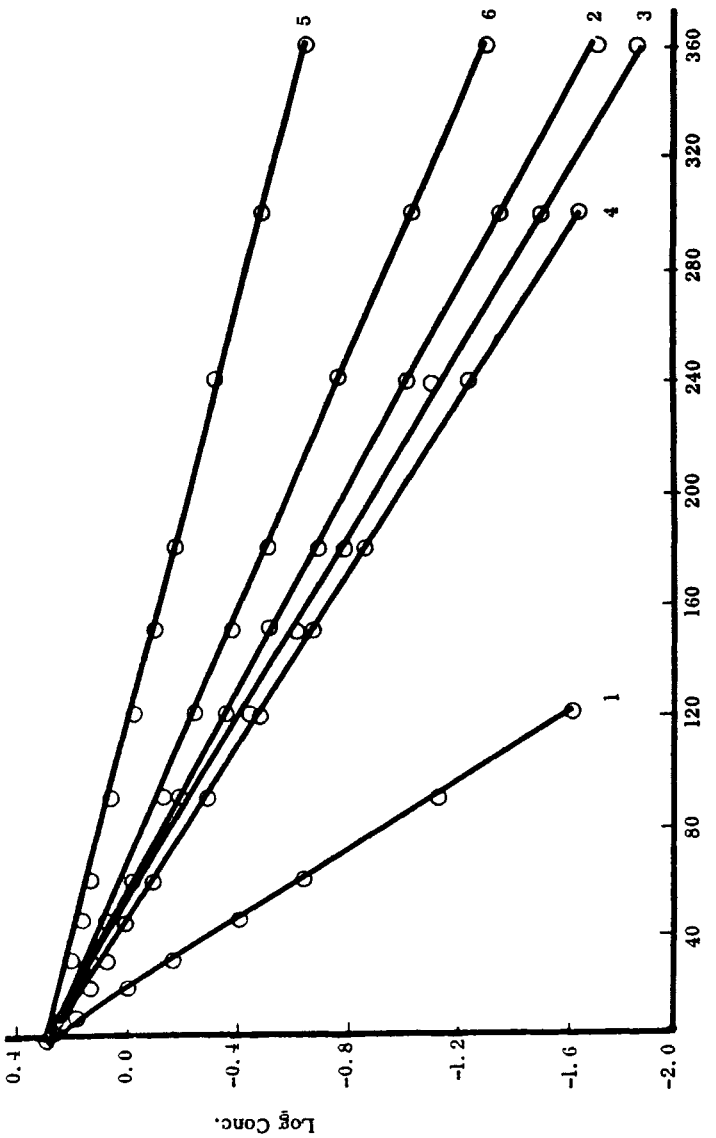

Figure 3. Apparent First Order Profile Effect of Thickening Agents on the Dialysis of Salicylate: Distilled Water/SIF.

Key: 1. Control 2. Natrosol 250J 3. CMHEC - 37M
4. Cellulose Gum 7MF 5. Methocel MC 400
6. Methocel MC 4000.

(Volume of gum solution incorporated: 20 ml.)

(Figure 3, Line 4), followed by another anionic gum, carboxymethylhydroxyethylcellulose (Figure 3, Line 3). In this study methylcellulose 400 and 4000 were most inhibitory to salicylate dialysis.

Slope, k and t_{50} values for the lines in Figures 1, 2 and 3 are listed in Table 1.

Table I. Slopes, k and t_{50} values for the dialysis of salicylic acid and salicylate in various gum vehicle combinations. (Figures 1, 2 and 3)

Vehicle Combinations	Slope of the Line	k (min^{-1})	t_{50} (min.)
15 ml. SGF + 5 ml. I(i)/SIF(o)	-0.0071	0.0163	42.4
15 ml. SGF + 5 ml. II(i)/SIF(o)	-0.0120	0.0270	25.7
15 ml. SGF + 5 ml. III(i)/SIF(o)	-0.0073	0.0170	41.0
15 ml. SGF + 5 ml. IV(i)/SIF(o)	-0.0085	0.0200	35.5
15 ml. SGF + 5 ml. V(i)/SIF(o)	-0.0082	0.0189	36.7
15 ml. SGF + 5 ml. VI(i)/SIF(o)	-0.0068	0.0156	44.3
15 ml. SGF + 5 ml. VII(i)/SIF(o)	-0.0066	0.0151	45.8
15 ml. SGF + 5 ml. H_2O(i)/SIF(o)	-0.0141	0.0326	21.3
20 ml. SGF/SIF(o)	-0.0100	0.0230	30.1
20 ml. I(pH 1.2)(i)/SIF(o)	-0.0009	0.0021	331.1
20 ml. II(pH 1.2)(i)/SIF(o)	-0.0023	0.0053	130.4
20 ml. IV(pH 1.2)(i)/SIF(o)	-0.0018	0.0042	165.5
20 ml. H_2O(i)/SIF(o)	-0.0160	0.0369	18.9
20 ml. I(i)/SIF(o)	-0.0026	0.0059	118.1
20 ml. II(i)/SIF(o)	-0.0043	0.0100	69.5
20 ml. IV(i)/SIF(o)	-0.0064	0.0147	47.3
20 ml. V(i)/SIF(o)	-0.0057	0.0132	52.5
20 ml. VII(i)/SIF(o)	-0.0056	0.0129	53.8

Figure 4 and Table II present the urinary excretion data following the oral administration of gum solutions containing sodium salicylate. Data for the 24th, 36th and 48th hours were not included since the urine salicylate values for the control and three gum dispersions were similar. The curves and tabulated data reveal the following:

(i) The Donnan effect is apparent *in vivo*. Thus the first hour's urine contained 8.2 ± 1.9% of the dose when a vehicle

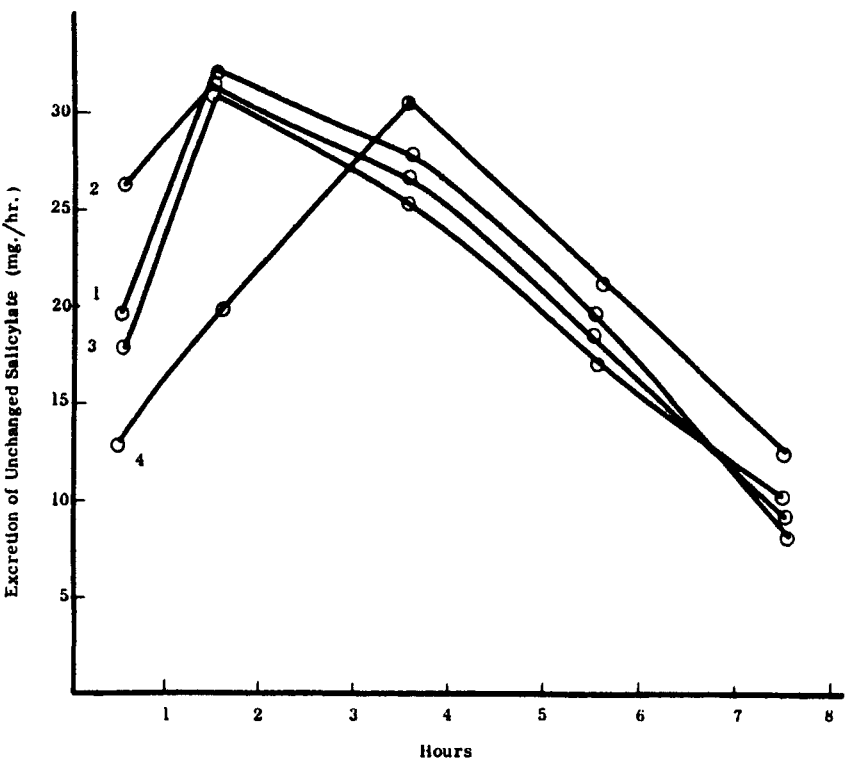

Figure 4. Urinary Excretion Rate of Salicylate as a Function of Time after Oral Administration of Sodium Salicylate Dissolved in Water and Aqueous Gum Dispersions.

Key: 1. Control 2. Cellulose Gum 7MF 3. Methocel MC 400 4. Methocel MC 4000.

Table II. Cumulative Urinary Excretion of Salicylate as a Function of Time After the Oral Administration of Sodium Salicylate (340 mg/20 ml. of Solution). (Average of 4 subjects ± S.D.)

Time (hrs)	Cumulative Per Cent of the Dose Excreted			
	Water	Methocel MC 400	Methocel MC 4000	CMC
1	5.4 ± 1.8	5.0 ± 0.7	4.4 ± 2.3	8.2 ± 1.9
2	14.9 ± 3.9	14.3 ± 3.1	9.5 ± 1.8	16.5 ± 2.5
4	30.7 ± 11.5	29.4 ± 6.8	27.0 ± 5.3	30.9 ± 2.9
6	41.9 ± 12.4	40.0 ± 9.2	39.1 ± 4.7	37.8 ± 4.7
8	46.9 ± 13.6	45.3 ± 8.8	46.3 ± 5.7	43.5 ± 2.7

containing sodium carboxymethylcellulose had been administered. Only 5.4 ± 1.8% of the dose was recovered at the end of one hour after the aqueous solution of sodium salicylate had been given. Statistical analysis of the data revealed that the probability that $\underline{t}$ will be within the limits of ± 1.93 is between 0.9 to 0.95. There was no significant difference between urinary recovery of salicylate at the end of the first hour for the methylcellulose 400 and 4000 as compared with the aqueous solution.

(ii) Methylcellulose 4000 delayed the oral absorption of salicylate since peak excretion occurred at 3.5 hours (Figure 4, Curve 4).

(iii) The areas under the curves (Figure 4) and the cumulated salicylate excretion (Table II) were similar.

Thus it has been shown that an anionic gum, such as sodium carboxymethylcellulose, is capable of accelerating the rate of absorption of an anionic drug, such as sodium salicylate.

It is realized that in view of the complexity of the systems investigated and the limited number of cases examined, care must be exercised in drawing firm conclusions from the results presented. However, from the data generated, more detailed studies should establish the significance of the observations made.

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FOOTNOTES

1. Mallinckrodt Chemical Works, St. Louis, Mo.
2. Methocel MC 400, Dow Chemical Co., Midland, Mich.
3. Methocel MC 4000, Dow Chemical Co., Midland, Mich.
4. Methocel 65 HG 400, Dow Chemical Co., Midland, Mich.
5. CMC-7 MF, Hercules, Inc., Wilmington, Del.
6. CMHEC-37 M, Hercules, Inc., Wilmington, Del.
7. Klucel GF, Hercules, Inc., Wilmington, Del.
8. Natrosol 250 J, Hercules, Inc., Wilmington, Del.
9. J.T. Baker Chemical Co., Phillipsburg, N.J.
10. Merck & Co., Inc., Rahway, N.J.
11. Methocel Brochure, Dow Chemical Co., Midland, Mich.
12. Waring Products Division, New Hartford, Conn.
13. Brookfield Engineering Laboratories, Inc., Stoughton, Mass.
14. Fisher Seamless Cellulose Dialyzing Tubing, Fisher Scientific Co., Pittsburgh, Pa.
15. Blue M Electric Co., Blue Island, Ill.
16. Coleman Instruments Corp., Maywood, Ill.

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