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Influence of Viscosity on Absorption from Nitrofurantoin Suspensions

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Abstract □ Nitrofurantoin, 200 mg, was administered orally to 11 subjects in an aqueous reference dispersion and in five suspensions having the same rheogram. Algin, carbomer, guar gum, methylcellulose, and colloidal magnesium aluminum silicate were the five suspending agents employed. Complexation was demonstrated by dialysis between nitrofurantoin and methylcellulose and between nitrofurantoin and carbomer; however, physiological availability was not altered by the interaction. The viscosity increase slowed absorption and urinary excretion, thus delaying the time of the maximum excretion rate without a decrease in bioavailability. A clinically acceptable urinary nitrofurantoin concentration was maintained for at least 2 hr longer by a viscosity increase.

Keyphrases □ Nitrofurantoin—suspensions, effect of viscosity on absorption □ Suspensions—nitrofurantoin, effect of viscosity on absorption □ Bioavailability—nitrofurantoin suspensions, effect of viscosity on absorption □ Antibacterial agents—nitrofurantoin suspensions, effect of viscosity on absorption

Based on the few literature reports, it is difficult to generalize the effect of viscosity on the absorption and availability of medicinal compounds from oral liquids. Malone *et al.* (1) noted that increasing viscosity by increasing the concentration of sucrose in aqueous solutions of phenobarbital sodium progressively lengthened the induction time of narcosis in rats. Davison *et al.* (2) found that methylcellulose delayed the absorption from orally administered sodium salicylate solutions as demonstrated by the reduction of brain and plasma salicylate levels.

Levy and Jusko (3) concluded that the decrease in absorption by the ligated rat stomach of alcohol and salicylic acid from solutions containing methylcellulose was due to the slower movement of the drug molecule to the absorbing membrane. Harper and Wordan (4) reported that the LD_{50} values of isoniazid (isonicotinic acid hydrazide) in rats were 3300, 2650, and 2000 mg/kg in acacia solution, gelatin solution, and water, respectively, and they concluded that the apparent toxicity was influenced by the vehicle. Hewitt and Levy (5) reported that, contrary to expectation, the oral administration of thiamine and riboflavin in highly viscous methylcellulose solutions did not affect the rate and extent of absorption. Ashley and Levy (6) showed that the absorption of phenolsulfonphthalein was decreased during the 1st hr by the addition of algin (sodium alginate) to the solution but that the total amount absorbed was unchanged.

BACKGROUND

Suspending agents are added to suspensions to increase the viscosity so that the sedimentation rate is slowed and the measurement of a proper dose is simplified. Because a suspending agent improves the physical properties of a suspension, it may concomitantly affect the absorption of the medicinal compound by the increased viscosity or by complexation. It has been shown that the dissolution rate of a solid is inversely proportional to the viscosity of the dissolution medium (7).

Since the dissolution rate often is the limiting factor in availability of a relatively insoluble medicinal compound in an orally administered suspension, viscosity would be expected to affect absorption. Seager (8) found that methylcellulose affected the excretion after the oral administration of a nitrofurantoin suspension so that less nitrofurantoin was excreted and the time of maximum excretion was delayed by 1 hr.

This study was conducted to determine, by a urinary recovery technique, the effect of suspending agents (algin, carbomer, guar gum, methylcellulose, and colloidal magnesium aluminum silicate) on the absorption of nitrofurantoin. Because the main concern was to determine if the viscosity affected GI absorption, all formulations containing a suspending agent had the same viscosity.

EXPERIMENTAL

Suspension Preparation—Nitrofurantoin[1] was classified by a sonic sifter[2], and the 70–140-mesh fraction (157 μm) was used. Nitrofurantoin, 200 mg, was dispersed in 20 g of vehicle. Each vehicle was prepared by making dispersions of various concentrations of the suspending agent, and their viscosities were measured by a rotational viscometer[3]. Guided by these results, more appropriate concentrations then were prepared, and their viscosities were measured. For each suspending agent, a concentration was found experimentally that provided a rheogram similar to that of a 2% aqueous solution of methylcellulose, 4000 cps.

Dialysis—Dialysis was carried out at 37° in cellophane tubing[4] tied into a sac with distilled water as the dialysis medium. The nitrofurantoin dispersion, 50 ml, was placed in the cellophane sac, which was soaked previously for 24 hr to achieve hydration; then the open end was tied. The sac was immersed in 100 ml of distilled water, sealed in the container, and attached to a submersion rotator[5].

At 3, 6, 12, 24, and 36 hr, one dialysis sac of a series was removed, fluid volume inside and outside of the sac was measured, and the nitrofurantoin concentration in the fluid inside and outside of the sac was determined from spectrophotometric measurements at 367 nm. Equilibrium was always attained in <36 hr.

Protocol—All suspensions were coded and distributed according to the Latin square law (9) so that two of the initial 12 volunteers received

[1] Lot 43C-1550, Sigma.
[2] Allen-Bradley.
[3] Brookfield LVT.
[4] Fisher 8-667E dialyzer tubing, 2.74 cm i.d.
[5] Model SR-25V, Scientific Industries.

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Table I—Mean Excretion Rate (±*SD*) and Mean Cumulative Milligrams (±*SD*) of Nitrofurantoin Excreted for 11 Subjects after Oral Administration of an Aqueous Reference Dispersion and Aqueous Suspensions Containing Various Suspending Agents

Hours	Reference Dispersion		Methylcellulose Suspension		Colloidal Magnesium Aluminum Silicate Suspension	
	Rate, mg/hr	Cumulative Excretion, mg	Rate, mg/hr	Cumulative Excretion, mg	Rate, mg/hr	Cumulative Excretion, mg
1	8.44 ± 9.82	8.44 ± 9.82	0.12 ± 6.75	6.12 ± 6.75	3.25 ± 3.49	3.25 ± 3.49
2	11.17 ± 4.08	19.61 ± 12.64	13.03 ± 8.00	19.15 ± 12.22	8.23 ± 6.49	11.48 ± 9.77
3	15.32 ± 5.76	34.93 ± 14.23	13.06 ± 6.60	32.21 ± 14.67	9.17 ± 3.36	20.65 ± 11.68
4	9.13 ± 6.34	44.06 ± 14.57	7.55 ± 5.00	39.76 ± 13.09	9.24 ± 5.16	29.89 ± 10.86
5	6.05 ± 4.34	50.11 ± 14.54	5.75 ± 5.88	45.51 ± 11.64	10.75 ± 7.73	40.64 ± 8.47
6	3.38 ± 3.03	53.49 ± 13.88	3.21 ± 5.39	48.73 ± 12.90	6.77 ± 6.58	47.41 ± 10.04
7	0.73 ± 0.67	54.22 ± 13.00	1.59 ± 2.09	50.32 ± 13.57	3.97 ± 5.30	51.38 ± 12.13
8	0.34 ± 0.21	54.56 ± 13.00	0.44 ± 0.38	50.76 ± 10.31	1.90 ± 3.97	53.28 ± 13.25
9	0.14 ± 0.12	54.70 ± 13.32	0.64 ± 1.27	51.40 ± 10.85	0.49 ± 0.42	53.77 ± 14.55
10	0.09 ± 0.11	54.79 ± 13.66	0.22 ± 0.23	51.62 ± 11.62	0.21 ± 0.16	53.98 ± 10.45
11	0.08 ± 0.08	54.87 ± 8.41	0.30 ± 0.40	51.92 ± 7.76	0.11 ± 0.06	54.09 ± 12.84
12	0.05 ± 0.03	54.92 ± 0.06	0.37 ± 0.48	52.29 ± 0.07	0.12 ± 0.02	54.21 ± 4.04
	Algin Suspension		Carbomer Suspension		Guar Gum Suspension	
Hours	Rate, mg/hr	Cumulative Excretion, mg	Rate, mg/hr	Cumulative Excretion, mg	Rate, mg/hr	Cumulative Excretion, mg
1	5.74 ± 4.72	5.74 ± 4.72	3.19 ± 3.38	3.19 ± 3.38	6.37 ± 6.64	6.37 ± 6.64
2	11.18 ± 8.34	16.92 ± 15.19	10.38 ± 7.38	13.57 ± 10.31	13.10 ± 8.79	19.47 ± 14.76
3	14.01 ± 6.34	30.93 ± 16.14	16.14 ± 8.29	29.71 ± 17.95	15.35 ± 7.94	34.82 ± 17.22
4	14.00 ± 8.30	44.93 ± 17.27	13.68 ± 5.19	43.39 ± 19.41	15.33 ± 9.79	50.15 ± 22.34
5	9.30 ± 5.66	54.23 ± 19.97	13.15 ± 6.11	56.54 ± 17.41	8.12 ± 6.27	58.27 ± 23.66
6	5.26 ± 4.31	59.49 ± 13.07	5.45 ± 6.14	16.99 ± 20.00	4.72 ± 5.76	62.99 ± 23.68
7	2.96 ± 4.08	62.45 ± 10.80	2.12 ± 2.85	64.11 ± 22.39	2.22 ± 4.52	65.21 ± 23.60
8	2.54 ± 5.91	64.99 ± 9.71	0.70 ± 1.09	64.81 ± 23.47	1.61 ± 3.08	66.82 ± 28.04
9	3.85 ± 7.36	68.84 ± 14.57	0.33 ± 0.49	69.14 ± 21.68	0.59 ± 0.98	67.41 ± 20.46
10	1.50 ± 3.00	70.34 ± 17.31	0.15 ± 0.18	65.29 ± 22.90	0.16 ± 0.10	67.57 ± 28.81
11	1.10 ± 1.87	71.44 ± 19.00	0.15 ± 0.08	65.44 ± 26.78	0.08 ± 0.09	67.65 ± 31.09
12	0.47 ± 0.49	71.91 ± 22.35	0.14 ± 0.06	65.58 ± 26.00	0	67.65 ± 31.05

Table II—Mean Time (±*SD*) of the Maximum Excretion Rate and Mean Percent (±*SD*) of the Oral Dose Excreted in 12 hr for 11 Subjects

Preparation	Maximum Rate, hr	Percent Oral Dose Excreted
Aqueous reference	2.6 ± 0.8	27.5 ± 6.9
Methylcellulose	2.9 ± 1.4	26.1 ± 6.5
Colloidal magnesium aluminum silicate	4.0 ± 1.7	27.1 ± 6.5
Algin	4.0 ± 1.6	35.9 ± 8.0
Carbomer	4.0 ± 1.3	32.9 ± 11.7
Guar gum	3.8 ± 0.7	33.8 ± 12.0

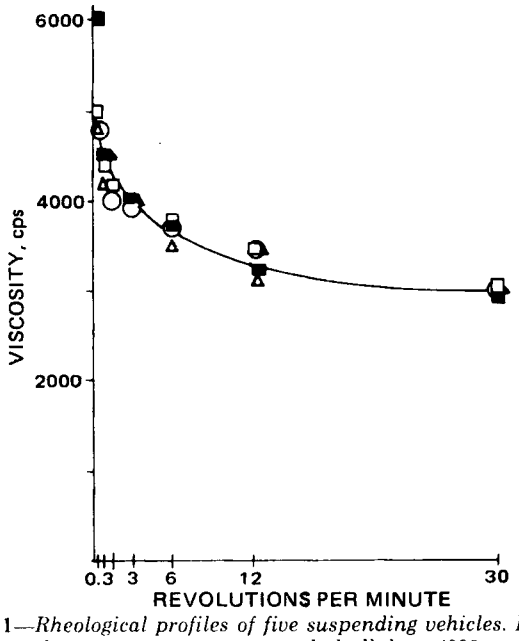

Figure 1—*Rheological profiles of five suspending vehicles. Key:* □, *algin;* △, *carbomer;* ■, *guar gum;* ○, *methylcellulose, 4000 cps; and* ▲, *colloidal magnesium aluminum silicate.*

the same suspension. Two weeks elapsed between each urinary study. One subject did not complete the study; the study was completed with two healthy female and nine healthy male subjects, 24–35 years old and 40–70 kg.

Each subject drank 300 ml of water upon arising. After 30 min, the bladder was voided, and the suspension was swallowed. The participants were instructed to allow adequate time for the suspension to drain from the container. Two 5-ml portions of water were used to rinse any residue from the container, and each portion was swallowed. No food or fluids were ingested for 6 hr.

Urine samples were collected at 1-hr intervals for 12 hr. Volumes were measured, and aliquots were retained in amber vials for analysis. The urinary pH was determined at the time of each sample collection, and the values ranged from 5.3 to 7.0. For a given subject, the pH fluctuation did not exceed 1 pH unit. No attempt was made to control the urinary pH.

Analytical Method—The urine analysis was carried out in duplicate by the method of Conklin and Hollifield (10) on the collection day. To protect the nitrofurantoin from light, amber glassware was used.

Statistics—The significance of the difference between suspensions containing different suspending agents and the reference dispersion was calculated using the Student two-tailed t test ($p = 0.05$).

RESULTS AND DISCUSSION

To compare the effect of several suspending agents on the absorption and urinary excretion of nitrofurantoin from an oral suspension, the viscosity should be the same for all suspensions. A 2% aqueous solution of methylcellulose, 4000 cps, was selected because it had a moderately high viscosity. This selection accented the factor of viscosity, but the suspension was pourable from the container. Figure 1 shows that the rheological characteristics of a 1.6% algin[6] solution, a 0.3% carbomer[7] solution, a 1.0% guar gum[8] solution, a 2.0% methylcellulose[9] solution, and a 5.0% colloidal magnesium aluminum silicate[10] dispersion are similar.

Shah and Sheth (11) demonstrated *in vitro* that the dialysis rate of nitrofurantoin was reduced by the presence of methylcellulose. They thought that this effect was due to the drug complexation in solution with

[6] Kelgin M.V., Kelco Co.
[7] Carbopol 934, B. F. Goodrich Chemical Co.
[8] Supercol GF, Henkel Co., General Mills Chemicals.
[9] Methocel 90 HG Premium, 4000 cps, Dow Chemical Co.
[10] Veegum, R. T. Vanderbilt Co.

Table III—Mean Nitrofurantoin Concentration in the Urine of 11 Subjects after Oral Administration of 200 mg of Nitrofurantoin

	Urinary Concentration					
Hours	Reference Dispersion	Algin Suspension	Carbomer Suspension	Guar Gum Suspension	Methylcellulose Suspension	Colloidal Magnesium Aluminum Silicate Suspension
1	1:12,000	1:25,000	1:50,000	1:20,000	1:25,000	1:50,000
2	1:8400	1:7700	1:9000	1:5500	1:10,000	1:10,000
3	1:4400	1:5000	1:5000	1:5000	1:10,000	1:10,000
4	1:5600	1:5000	1:5000	1:5000	1:10,000	1:10,000
5	1:8300	1:5000	1:5000	1:6600	1:10,000	1:10,000
6	1:15,000	1:11,100	1:8300	1:11,100	1:20,000	1:11,100
7	1:126,000	1:15,100	1:33,300	1:33,300	1:33,300	1:14,200
8	1:200,000	1:17,200	1:100,000	1:50,000	1:125,000	1:33,300
9	1:357,000	1:14,200	1:140,800	1:200,000	1:90,000	1:142,800
10		1:52,600				
11		1:52,600				
12		1:125,000				

the polymer. A nitrofurantoin–suspending agent interaction (complexation) possibly could affect absorption and urinary excretion. Nitrofurantoin and each suspending agent were dialyzed until equilibrium was attained. Aqueous dispersions of nitrofurantoin with carbomer and with methylcellulose gave ratios of the concentration in the internal compartment to that in the external compartment of 1.22 and 1.26, respectively, thus indicating interaction between nitrofurantoin and carbomer and between nitrofurantoin and methylcellulose such that less nitrofurantoin diffused through the membrane. Such an interaction could interfere with absorption and subsequent urinary excretion. No interaction occurred with algin, guar gum, and colloidal magnesium aluminum silicate.

In a blind study, 11 subjects ingested 200 mg of nitrofurantoin in various suspensions of the same viscosity and in an aqueous dispersion at 2-week intervals. No nitrofurantoin was detected in the urine of any subject after 12 hr. The half-life was determined by plotting the logarithm of the amount excreted after administration of the aqueous dispersion against time (12). The average half-life was 1.03 ± 0.45 hr. This result agrees with the literature values that range from 0.3 to 1.0 hr (13).

The excretion rate and the cumulative milligrams excreted were determined and plotted for each subject. From these data, the percent of the orally administered dose excreted in the urine and the time of the maximum excretion rate were determined for each subject. Data for each individual are not given to conserve space. The mean ($\pm SD$) excretion rate and the cumulative amount ($\pm SD$) excreted for 11 subjects are given in Table I for the aqueous reference dispersion and for the five suspensions. Figure 2 shows the mean cumulative amount of nitrofurantoin excreted as a function of time for each suspension.

The mean percent ($\pm SD$) of the oral dose excreted is given in Table II. The significance of the difference between the aqueous reference dispersion and the means in Table II was calculated using the Student t test. The percent of the oral dose recovered in the urine was not diminished significantly by any suspending agent, even though *in vitro* interaction had been demonstrated between nitrofurantoin and methylcellulose and between nitrofurantoin and carbomer. This result indicates that under physiological conditions, complexation, as demonstrated by dialysis, does not interfere with GI absorption. Because complexation did not alter physiological availability, any changes in urinary excretion may be attributed to the effect of viscosity.

The excretion rates were plotted against time for each subject. The times of the maximum excretion rate for each of the 11 subjects were averaged to give the mean time ($\pm SD$) of the maximum excretion rate given in Table II. The significance of the difference between the mean time of the maximum excretion rate of the aqueous reference dispersion and the suspensions with various suspending agents (Table II) was determined using the Student t test. The differences between the time of the maximum excretion rate of the aqueous reference dispersion and the test suspensions were significant.

Nitrofurantoin suspended with methylcellulose reportedly (8) delays the maximum absorption time by 1 hr relative to an aqueous reference dispersion. In this study, the time at which the average maximum excretion rate occurred for the preparation containing methylcellulose was only 0.3 hr longer than that of the aqueous reference dispersion, with the time of the maximum excretion rate varying from 1 to 6 hr for the 11 subjects. The reason for this wide variation without a significant difference between the aqueous reference dispersion and the suspension containing methylcellulose is unknown.

As shown in Table II, the mean time of the maximum excretion rate was increased by 1.4 hr for the experimental viscosity induced by algin, carbomer, guar gum, and colloidal magnesium aluminum silicate in comparison to an aqueous dispersion. Thus, the increased viscosity of these oral suspensions delayed absorption and excretion but did not diminish total absorption. Since increasing viscosity slows diffusion, mobility, and the dissolution rate, one would anticipate slower absorption and excretion.

Because nitrofurantoin is rapidly excreted in the urine, slower absorption could maintain a clinically recommended concentration of 1:100,000-1:200,000 (14) in the urine for a longer time. The mean nitrofurantoin concentration in the urine of 11 subjects after the oral administration of 200 mg of nitrofurantoin is given in Table III. With 1:100,000 as the nitrofurantoin concentration needed for the clinically acceptable bacteriostatic effect, the reference dispersion is acceptable for 6 hr. The suspensions containing carbomer, guar gum, and colloidal magnesium aluminum silicate are acceptable for 8 hr. The suspensions containing methylcellulose and algin are acceptable for 7 and 11 hr, respectively.

An increase in viscosity of the investigated suspensions delayed absorption; consequently, urinary excretion was delayed without a decrease in availability. As a result, the concentration in the urine was maintained

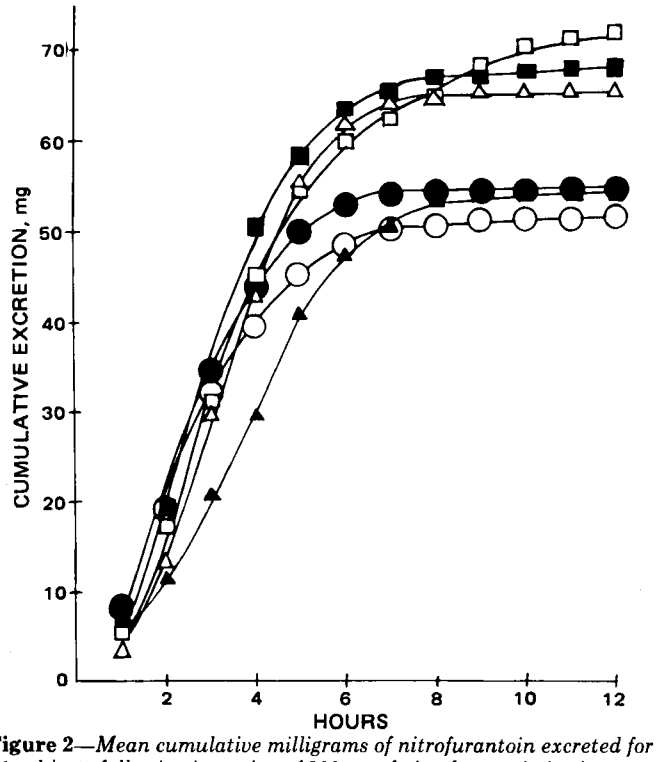

Figure 2—*Mean cumulative milligrams of nitrofurantoin excreted for 11 subjects following ingestion of 200 mg of nitrofurantoin in six preparations. Key: ●, aqueous reference dispersion; □, algin; △, carbomer; ■, guar gum; ○, methylcellulose, 4000 cps; and ▲, colloidal magnesium aluminum silicate.*

at a clinically useful concentration for a longer time. In the studied suspensions, the viscosity maintained an acceptable concentration in the urine for at least 2 hr longer than that obtained from an aqueous dispersion.

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Surface Properties of Membrane Systems: Interaction of Electrolyte and Lipid with Ca^{2+} Ionophores

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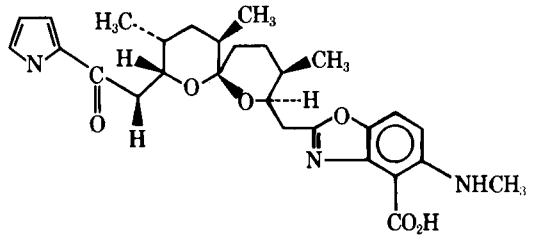
Abstract □ When spread from organic solvents onto electrolyte solutions, the Ca^{2+} ionophores A23187 (I) and X537A (II) formed films with relatively high surface pressures and surface potentials. Ionophore I had collapse pressures between 16 and 19 dynes/cm and nearly equal surface activity on distilled water and on 1000 mEq of either sodium chloride or calcium chloride. Film pressure did not reveal appreciable ion selectivity. However, the surface potential of I on calcium chloride solution was higher than that on sodium chloride, and the potential difference, $\Delta(\Delta V)$, of 40 mv was independent of the electrolyte concentration. In contrast, the ion selectivity of II was dependent on the electrolyte concentrations since the $\Delta(\Delta V)$ value between calcium chloride and sodium chloride was maximal (130 mv) on 1000 mEq and negligible on 500- and 2000-mEq salt solutions. The isotherms of phospholipid–ionophore films were markedly different from those of the individual components, although they revealed ionophore characteristics at low film pressures and phospholipid behavior at high film pressures. The magnitude of the surface potential indicated that dipalmitoyl phosphatidylcholine enhanced, whereas mitochondrial lipid and cardiolipin reduced, the preference of the two ionophores for Ca^{2+} over Na^+. Since the ion selectivity was manifested most at both high electrolyte and high lecithin concentrations, the ionophore probably prefers the low dielectric constant of neutral lipid membranes to complex with the selected cation.

Keyphrases □ Membrane systems—surface properties, interaction of electrolytes and lipids with Ca^{2+} ionophores □ Surface pressure—films of Ca^{2+} ionophores on electrolyte solutions, effect of membrane lipids □ Surface potential—films of Ca^{2+} ionophores on electrolyte solutions, effect of membrane lipids □ Ionophores, Ca^{2+}—surface properties of films on electrolyte solutions, effect of membrane lipids

The ubiquitous occurrence and importance of Ca^{2+} in biological processes (enzymatic as well as mechanical) prompt interest in the modes of its availability, translocation, and action. The transport of ions in and out of cells may be aided by certain organic molecules, referred to as ionophores (1). These molecules are expected to influence metabolic (2) and physical (3) properties of cells in culture as well as *in vivo*.

Questions have been raised as to whether and how Ca^{2+} may stimulate or inhibit specific membrane and intracellular enzymes (4) and the contractile activity of systems within both the plasma membrane and the cytoplasm. Although extensive work has been published on the physicochemical properties of numerous ionophores and their interactions with natural and artificial membranes (1), little is known about the surface behavior of the Ca^{2+} ionophores A23187 (mol. wt. 523, I) and X537A (mol. wt. 590, II); this information is important since at least some of the action of the ionophore develops at membranes, whose structure and function are controlled by surface phenomena.

As in the case of valinomycin (5, 6), surface activity and surface potential should reflect certain structural char-



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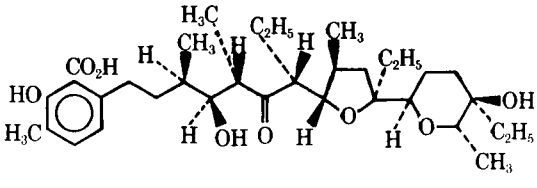

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