Attempts to correlate the catalytic effects of HB^- with that predicted from the Brönsted relation (8) are complicated by the dual nature of the catalyst which is defined here as participating both as an acid and a base. The values for the predicted catalytic constants, k_A (or k_B), in terms of G_A and α(or G_B and β) can be compared for each type of buffer species since the Brönsted relation is well obeyed within a group of similar catalytic species such as H_nB, $H_{n-1}B^-$, B^{2-}, *etc.* The value of the experimental catalytic constant for a potentially catalytic species, X, can also be calculated from $k_X = k_{cat.}$ [cat.]/(concn. X). (See Table III.) The assumption in this latter calculation is that one catalytic species predominates in each buffer as has been demonstrated for the phosphate system. The data were treated in this manner and the results, while not conclusive, are consistent with the present hypothesis. The catalytic constants as calculated from the data were compared to the catalytic constants as calculated from the Brönsted relation using the statistical correction and assigning a value of 0.5 to α or β. The only good correlation evident was that between k_{Hn-1B^-} and the values of k_A (in terms of G_A) for the species $H_{n-1}B^-$. This result is consistent with the choice of HB^- as the primary catalytic species. The fact that the correlation exists for k_A in this comparison and not for k_B implies that the catalytic species requires a donatable proton. The formate, lactate, and acetate ions, which exhibit no significant buffer effect as seen in Table III, also have no value for k_A since the anions cannot act as proton donors.

It can be concluded from the above discussion that the mechanism offered in Scheme I is consistent with the experimental data presented here as well as the related data of the other workers cited above.

SUMMARY

Consideration of the 1,4-addition products formed from the reaction between bisulfite and cytosine arabinoside and consideration of the effects of phosphate, oxalate, succinate, lactate, formate, and acetate buffers has demonstrated that cytosine deamination will be significantly catalyzed by a nucleophile bearing a donatable proton in the presence of hydrogen ions. The primary mechanism of hydrolytic deamination of cytosine nucleosides in aqueous catalytic buffer systems, as illustrated in Scheme I, is as follows: (*a*) protonation of N-3, (*b*) nucleophilic attack at C-6, (*c*) saturation at C-5 by proton addition, and (*d*) nucleophilic displacement at C-4 by H_2O with loss of NH_3.

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Effect of Some Nonionic Surfactants on the Rate of Release of Drugs from Suppositories

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Twenty-eight nonionic surfactants were added to theobroma oil base suppositories. The amount of aminophylline, ephedrine alkaloid, and ephedrine hydrochloride released from these bases was determined by dialyzing the released drug through a cellophane membrane and determining the optical absorbance at the appropriate wavelength. Data obtained indicate that surfactants with HLB values of less than 11 had little effect on the rate of release. Surfactants with HLB values over 11 increased significantly, in most cases, the amount of drug dialyzed. Besides HLB values, other properties of surfactants such as chemical structure, composition, and melting point also affect the rate of release.

THE USE OF suppositories as a form of medication dates back to the time of Hippocrates. Many unsatisfactory agents were tried as bases, but it was not until the discovery and development of theobroma oil as a base in the 18th century that they received much attention. In more recent days much attention has been directed toward modifying and improving bases of theobroma oil, glycerinated gelatin, and polyethylene glycol polymers, and in developing new bases. Until fairly recently, as long as the suppository retained its shape on the shelf, melted or dissolved in the rectum, and showed no visible evidence of incompatibility it was considered satisfactory. Recently it has been recognized

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that many factors may affect the action of the drug following administration of the suppository.

From the literature we have a plethora of conflicting reports as to the efficacy of suppository medication. Most clinical work has been done with aminophylline, hence this part of the discussion will be limited mainly to reports concerning aminophylline or theophylline. Segal *et al.* (1) compared the protection against intravenously administered histamine by aminophylline administered by various routes. They found that suppositories gave slightly less relief than intravenous administration but that relief persisted for a longer period of time. Tablets were slower acting and afforded less relief than either of the other two dosage forms. Waxler and Schack (2), on the other hand, found blood levels of aminophylline from suppositories to be much lower than those obtained from intravenous or intramuscular injection, or from uncoated oral tablets. However, blood levels from suppositories were sustained for longer periods of time, except for intramuscular injection. Truitt *et al.* (3) found retention enemas gave highest levels, except for intravenous administration, and that suppositories gave lowest blood levels of all methods tested. Glass *et al.* (4) obtained satisfactory blood levels of theophylline following administration of suppositories of a mannitol or a buffered polyethylene glycol base. Lower blood levels were obtained from other bases.

Drugs may be absorbed from the intestinal tract by three processes: (*a*) active transport, (*b*) passive transport, and (*c*) specialized transport. Passive transport, or diffusion, has been shown to be the method by which most drugs are absorbed. Brodie *et al.* (5) showed that once a drug is in solution in the gastrointestinal tract its passage through the gastrointestinal fluid and across the lipoidal membrane is governed mainly by physical processes and is often predictable, based on the partition coefficient of the undissociated drug moiety and the dissociation constant of the drug. Riegelman and Crowell (6) in their reports on rectal absorption obtained results which agree with the assumption that the limiting factor is the diffusion of the drug to the absorption site. Suppositories, or other dosage forms, which release the drug fastest to the surrounding medium should, theoretically, afford more rapid absorption by the body and higher blood levels of the drug.

The literature contains numerous reports (7–19) of the effects of surfactants on the rate of release of various medicaments from oils, fats, *etc.* This study was to determine the effects of various factors, particularly nonionic surfactants, on the rate of release of drugs from different suppository bases, primarily those composed of theobroma oil.

Since most clinical reports concern aminophylline (theophylline ethylene diamine), it was selected as the primary test drug. For comparative purposes, ephedrine alkaloid and one of its more water-soluble salts, ephedrine hydrochloride, were selected.

Since many of the bases contained surfactants and emulsified when in contact with water, it was necessary to use some means of separating the drug from the emulsified base of theobroma oil. Dialyzing the liberated drug through a cellophane membrane accomplished this separation, permitting determination of the amount of drug, although some ingredients of the base, particularly the surfactants, may have dialyzed also.

EXPERIMENTAL

Materials—Where possible, official products were used. Nonofficial products were of food or drug grade and were used as received from the manufacturer or distributor with no further purification. All theobroma oil was purchased at one time and all dialyzing membrane was from the same manufacturer.

Preparation of Suppositories—After calibration of the mold, 140 mg. of aminophylline, or 700 mg. of ephedrine or ephedrine hydrochloride, sufficient for 14 suppositories, was incorporated by geometric dilution into the just-melted base of theobroma oil and surfactant. After thorough mixing the mass was poured immediately into an unlubricated mold for 12 suppositories. The excess mass was used to prepare the melting point tubes or discarded. Blank suppositories—containing no drug—were prepared of each base to determine the absorbance of each base. The suppositories and melting point tubes were placed in a refrigerator at 5° for 2 days, then stored at room temperature for at least 3 days before testing. All suppositories were satisfactory in appearance and physical stability with no evidence of leakage, blooming, or color change for 3 months. After that time, several batches began to show a mottled appearance but looked satisfactory otherwise.

Procedure for Aminophylline—Dialyzing bags were prepared from dialyzing cellophane tubing, tied with cotton thread, and soaked overnight in distilled water before use. After rinsing the bags twice, 25 ml. of distilled water was placed in each bag which was then placed in a 500-ml. wide-mouth bottle containing 175 ml. of distilled water. The bottle was placed in a constant-temperature water bath at 39° and allowed to reach that temperature. This temperature was selected to ensure being above the clear melting point for all suppositories.

One suppository was placed in each bag which was suspended so that the level of the water inside was even with the level of the water outside the bag. The water in the bottle was stirred by a slowly turning coated magnet and a magnetic stirrer. At intervals a sample was removed from the bottle

and the absorbance at 273 mμ was determined using a Beckman model DB spectrophotometer. The concentration of aminophylline was obtained from a standard curve with corrections made for the absorbance of each suppository base (theobroma oil plus surfactants).

Procedure for Ephedrine and Ephedrine Hydrochloride—Since ephedrine and its salts passed through the dialyzing membrane very rapidly, it was necessary to modify the technique used previously. Instead of using a dialyzing bag, a cellophane membrane, previously soaked overnight and rinsed in distilled water, was stretched firmly over the open end of a thistle tube 38 mm. in diameter and made watertight by a rubber band.

After a suppository had been placed in the tube and the end closed as described, the inverted tube was suspended so that the membrane was just below the surface of 200 ml. of distilled water in a 500-ml. wide-mouth bottle. Water rapidly passed through the membrane and dissolved the drug. The bottle was immersed in a constant-temperature water bath at 39° and stirred by a slowly turning coated magnet and a magnetic stirrer. At intervals a sample was removed from the bottle and the absorbance at 257 mμ determined using a Beckman model DU spectrophotometer. The concentration of ephedrine or ephedrine hydrochloride was determined from the respective standard curve with corrections made for the absorption of the particular suppository base.

RESULTS AND DISCUSSION

Aminophylline—Table I shows the composition and melting range of various types of suppository bases selected to establish variations in rate of release and dialysis of aminophylline. The results of dialyzing the suppositories, shown in Table II, are in general agreement with previously published reports (7–19) on the rate of release of water-soluble substances from suppository bases. The addition of the hydrogenated vegetable oil to stabilize the melting point of theobroma oil greatly reduced the rate of release of aminophylline. The degree of

Table II—Aminophylline Dialyzed from Various Types of Suppository Bases

Base	Time, min. 15	30	60	120	180
	Aminophylline Dialyzed, mg.				
Theobroma oil	0.1	0.35	1.0	2.5	4.5
Theobroma oil–hydrogenated vegetable oil	Neg.[a]	Neg.[a]	0.08	0.3	0.5
Polyethylene glycol	0.5	0.9	2.0	4.3	6.1
Polysorbate 61	...	1.5	3.0	5.0	6.0
Anhydrous liquid	0.2	0.4	0.7	1.2	...
Petrolatum–paraffin	Neg.[a]	Neg.[a]	0.1	0.3	0.5
Adeps solidus base[b]	0.1	0.3	0.5	1.0	...
Aqueous soln., no base 10 mg./25 ml.	0.7	1.5	2.8	5.3	6.1

[a] Neg., negligible. [b] Marketed as Witepsol H12 by Chemische Werke Witten, Germany.

Table I—Composition and Melting Range of Various Types of Suppository Bases

Compn.		Melting Range
Theobroma Oil Base		
Theobroma oil	100%	32–33°
Theobroma Oil–Vegetable Oil		
Theobroma oil	97%	36–39°
Completely hydrogenated vegetable oil[a]	3%	
Theobroma Oil–Surfactant Bases		
Theobroma oil	95%	32–34° for all suppositories.
Surfactant	5%	
Polyethylene Glycol Base[b]		
Polyethylene glycol 4000	53%	Did not melt, but dissolved in test.
Polyethylene glycol 6000	47%	
Polysorbate 61 Base		
Polyoxyethylene sorbitan monolaurate (polysorbate 61)[c]	90%	Did not melt, but emulsified in test.
Glyceryl monolaurate	10%	
Anhydrous Liquid Base[d]		
Emulsifier[e]	5%	Liquid at room temperature; emulsified in water in test.
Polysorbate 80[f]	5%	
Silica[g]	4%	
Centrofil SM[h]	0.5%	
Liquid petrolatum, heavy	85.5%	
Petrolatum–Paraffin Base		
White petrolatum	75%	51–53°
Paraffin	25%	Did not melt in test.
Adeps Solidus Base		
Adeps solidus	100%	32–33.5°

[a] Marketed as Fix-X by Procter & Gamble. [b] Other proportions tried but no significant difference in results. [c] Marketed as Tween 61 by Atlas Chemicals Industries, Wilmington, Del. [d] Formula from Atlas Chemical Industries, Inc., Pharmaceutical Bulletin LD-99. [e] Marketed as Atmos 300 by Atlas Chemical Industries. [f] Marketed as Tween 80 by Atlas Chemical Industries. [g] Marketed as Cab-O-Sil by Cabot Corp. [h] Marketed as Centrofil SM by Central Soya Co. [i] Marketed as Witepsol H12 suppository base by Chemische Werke Witten, Germany, and contains varied proportions of saturated natural fatty acids.

Table III—Aminophylline Dialyzed from Theobroma Oil Containing 5% Nonionic Surfactants

Surfactant Chemical Type or Compn.	HLB	Time, min. 15	30	60	90
		Aminophylline Dialyzed, mg.			
Theobroma Oil only	0	0.1	0.35	1.0	1.6
Sorbitan Fatty Acid Esters[a]					
Sorbitan trioleate	1.8	...	0.8	1.9	2.7
Sorbitan monooleate	4.3	...	0.9	2.1	4.0
Sorbitan monostearate	4.7	...	0.3	1.2	2.5
Sorbitan monopalmitate	6.7	...	0.6	1.7	2.7
Sorbitan monolaurate	8.6	...	1.5	2.1	3.6
Polyoxyethylene Sorbitan Fatty Acid Ester-Ethers[b]					
POES monostearate	9.6	...	1.5	2.9	4.6
POES monooleate	10.0	...	0.7	2.1	...
POES tristearate	10.5	...	1.5	2.7	3.6
POES trioleate	11.0	...	0.8	2.4	3.4
POES monolaurate	13.3	...	2.4	4.1	5.1
POES monostearate	14.9	...	1.5	3.3	3.7
POES monooleate	15.0	...	1.0	2.5	3.5
POES palmitate	15.6	...	1.2	2.4	3.5
POES monolaurate	16.7	...	1.2	2.5	3.6
Polyoxyethylene Fatty Acid Esters[c]					
POE (8) stearate	11.1	1.7	6.0	9.5	...
POE (40) stearate	16.9	1.0	1.5	7.4	...
POE (50) stearate	17.9	1.1	1.7	8.1	...
Polyoxyethylene Fatty Ethers[d]					
POE (4) lauryl ether	9.7	1.7	2.6	9.8	...
POE (23) lauryl ether	16.9	...	1.8	6.6	...
POE (2) cetyl ether	5.3	0.3	0.6	1.3	...
POE (10) cetyl ether	12.9	1.1	2.0	7.8	...
POE (20) cetyl ether	15.7	0.8	0.9	2.6	...
POE (2) stearyl ether	4.9	0.4	0.6	1.1	...
POE (10) stearyl ether	12.4	1.2	2.1	7.4	...
POE (20) stearyl ether	15.3	0.5	1.0	2.1	...
POE (2) oleyl ether	4.9	0.9	1.7	5.2	...
POE (10) oleyl ether	12.4	1.2	2.2	8.1	...
POE (20) oleyl ether	15.3	0.7	1.5	5.6	...

[a] Marketed as Span 85, 80, 60, 40, and 20, respectively; [b] marketed as Tween 61, 81, 65, 85, 21, 60, 80, 40, 20, respectively; [c] marketed as Myrj 45, 52, and 53, respectively; [d] marketed as Brij 30, 35, 52, 56, 58, 72, 76, 78, 92, 96, and 98 respectively, by Atlas Chemical Industries, Wilmington, Del.

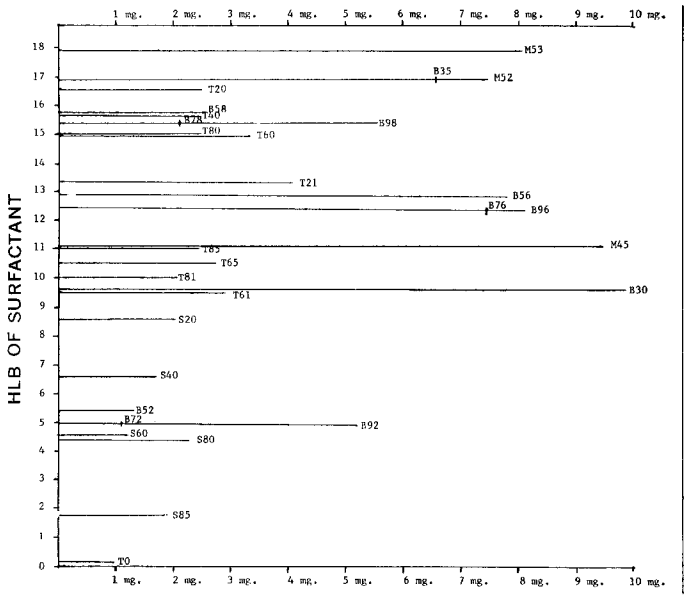

Fig. 1—Milligrams aminophylline dialyzed after 1 hr. Key: B, polyoxyethylene fatty ethers; M, polyoxyethylene fatty acid esters; S, sorbitan fatty acid esters; T, polyoxyethylene sorbitan fatty acid ester ethers; TO, theobroma oil.

interference with dialysis suggests that it was more than simply a matter of raised melting point.

Effect of HLB—To determine the effects of some nonionic surfactants in theobroma oil on the rate of release and dialysis, the various surfactants were incorporated as previously described. Table III shows the surfactants, grouped by chemical composition and type, which were added, and the amount of aminophylline dialyzed. Figure 1, with the surfactants arranged in descending order of HLB values, shows the amount of aminophylline dialyzed. In every case more aminophylline was dialyzed from the surfactant-containing base. Relatively uniform and moderate increases were noted from surfactants having an HLB value of less than 11, except for polyoxyethylene oleyl ether and polyoxyethylene lauryl ether.

Maximum drug was dialyzed from bases containing surfactants with HLB values of 11 to 14. Some surfactants with high HLB values (16–18) also released large amounts of drug. This agrees, in general, with other reports (9, 10, 12, 14, 19). Since the required HLB value of theobroma oil for an o/w emulsion is approximately 14 (20), it is to be expected that a surfactant with an HLB of about 14 would be most effective in emulsifying the theobroma oil, greatly increasing the oil–water interface.

Effect of Chemical Composition and Type—A comparison of those surfactants containing the C_{18} saturated moiety (stearic acid ester or stearyl alcohol ether) reveals that the polyoxyethylene fatty acid esters consistently dialyzed more aminophylline than the corresponding polyoxyethylene fatty ethers, sorbitan monostearate, or polysorbate 60, 61, or 65. As a group, the polyoxyethylene fatty acid esters gave best release even though their HLB values were not at 14. Part of the difference in amount dialyzed is undoubtedly due to HLB differences but apparently the ester linkage is superior to the ether linkage. Since stearate is the only radical common to all groups of surfactants, other groupings cannot be compared as completely.

A comparison of laurate or lauryl alcohol ether and oleate or oleyl alcohol ether reveals that the ethers were far superior to the sorbitans or polysorbates (esters or ester-ethers). The presence of sorbitan in the molecule consistently resulted in poor dialysis results. Under the conditions of the test (suppository bases emulsified) it was not possible to determine whether the poor results were due to slow release of the aminophylline from the suppository or whether it was released but not dialyzed. It is probable that the large sorbitan molecule hindered passage of the drug through the membrane.

Examination of the results from the surfactants containing fatty alcohols with equivalent-length polyoxyethylene chains and equivalent HLB values shows that the stearyl alcohol ethers dialyzed the released aminophylline most slowly, followed by cetyl, oleyl, and lauryl alcohol ethers, respectively. The melting range of each suppository base was determined by the U.S.P. XVI method for class II substances (21). All melting ranges were between 32–34°, well below the test temperature, with no consistent pattern due to surfactant. It appears from the results that the more saturated hydrocarbons with higher melting points inhibit the dialysis of aminophylline either by slightly raising the melting point or possibly by complexing with the drug. The former is in general agreement with the finding of Eckert and Muhlemann (15), who reported that at temperatures above the clear melting point of suppositories the rate of release increases enormously for water-soluble drugs, and the rate of diffusion reaches the values of a corresponding aqueous solution.

The increased rate of dialysis of aminophylline from theobroma oil suppositories to which the surfactants were added was probably due to several factors. Apparently the surfactants, acting as solubilizing agents, increased the solubility of aminophylline in water, or they increased the rate of solution by emulsifying the base, thereby increasing the

oil–water interface. It is also possible that they affected the dialyzing membrane, rendering it more permeable to the aminophylline.

It is probable that an intermolecular reaction or binding occurred between the aminophylline and the surfactant or that the drug was trapped within the micelles, especially those containing the sorbitan moiety. The evident difference in amounts dialyzed with those surfactants containing sorbitan indicates a slowdown, which is probably due to the formation of a large, slowly diffusible and dialyzable particle. Recently Kakemi *et al.* (22) have reported reduced absorption of several sulfonamides when nonionic surfactants were added to aqueous solutions of the sulfonamides. They theorized that the sulfonamide was trapped within the micelles of the surfactant and the large molecule passed slowly through the rectal membrane.

Ephedrine and Ephedrine Hydrochloride—Table IV summarizes the milligrams of both ephedrine and ephedrine hydrochloride dialyzed after 30 min. and 1 hr. For ephedrine hydrochloride, equilibrium was approached after 1 hr. For ephedrine, equilibrium was not reached after 24 hr. for all bases. For comparative purposes, the dialysis of the drugs from theobroma oil with no surfactant is shown at the top of the table.

Ephedrine Hydrochloride—Figure 2, with the surfactants arranged in descending order of HLB values, shows the amount of ephedrine hydrochloride dialyzed. The moderate increases noted were much less than the increases reported for aminophylline.

TABLE IV—EPHEDRINE AND EPHEDRINE HYDROCHLORIDE DIALYZED FROM THEOBROMA OIL CONTAINING 5% NONIONIC SURFACTANTS

Surfactant Chemical Type or Compn.[a]	HLB	Time, min. 30	60	30	60
		Ephedrine HCl Drug Dialyzed, mg.		Ephedrine	
Theobroma Oil	0	25	31	9	14
Sorbitan Fatty Acid Esters					
Sorbitan trioleate	1.8	32	35	9	13
Sorbitan monooleate	4.3	26	31	6	9
Sorbitan monostearate	4.7	15	27	5	8
Sorbitan monopalmitate	6.7	18	25	6	10
Sorbitan monolaurate	8.6	..	..	..	..
Polyoxyethylene Sorbitan Fatty Acid Ester-Ethers					
POES monostearate	9.6	35	41	12	17
POES monooleate	10.0	33	37	9	14
POES tristearate	10.5	29	35	7	11
POES trioleate	11.0	29	32	7	12
POES monolaurate	13.3	35	40	12	18
POES monostearate	14.9	36	42	13	18
POES monooleate	15.0	33	42	17	21
POES palmitate	15.6	22	27	17	23
POES monolaurate	16.7	37	41	14	19
Polyoxyethylene Fatty Acid Esters					
POE (8) stearate	11.1	41	42	10	15
POE (40) stearate	16.9	36	40	14	20
POE (50) stearate	17.9	32	35	14	20
Polyoxyethylene Fatty Ethers					
POE (4) lauryl ether	9.7	40	43	8	13
POE (23) lauryl ether	16.9	32	34	12	17
POE (2) cetyl ether	5.3	30	33	8	12
POE (10) cetyl ether	12.9	39	41	10	17
POE (20) cetyl ether	15.7	33	37	13	18
POE (2) stearyl ether	4.9	31	35	8	10
POE (10) stearyl ether	12.4	37	42	13	19
POE (20) stearyl ether	15.3	33	39	12	17
POE (2) oleyl ether	4.9	27	30	8	12
POE (10) oleyl ether	12.4	39	41	10	17
POE (20) oleyl ether	15.3	33	39	13	19

[a] See footnotes to Table III.

Those surfactants having an HLB value of less than 9 had little effect, some slightly decreased the amount dialyzed. It is possible that the surfactant complexed or reacted with the drug or trapped the drug within the micelles, but the evidence is not conclusive as three of the surfactants, sorbitan monopalmitate and sorbitan monostearate, and POE (2) oleyl ether decreased dialysis and four, sorbitan monooleate and sorbitan trioleate, and POE (2) cetyl ether and POE (2) stearyl ether, had no effect or slightly increased the amount dialyzed. Above an HLB value of 9, the surfactants, with the exception of polysorbate 40, increased slightly the amount dialyzed. The increases were probably due to either an increased solubility of ephedrine hydrochloride or, more probably, to an increased rate of solution of the salt due to the formation of an o/w emulsion, thus increasing the oil–water interface. Below an HLB value of 9, a w/o emulsion formed in which the dissolved or released drug remained inside the oil (external phase).

Ephedrine Alkaloid—Figure 3 shows the amount of ephedrine dialyzed. As expected, due to its more lipid solubility, much less alkaloid was dialyzed than the corresponding hydrochloride salt. Much the same general pattern of dialysis was noted as with ephedrine hydrochloride, with several exceptions. Maximum ephedrine dialyzed from the polysorbate 40-containing base but less ephedrine hydrochloride dialyzed than from theobroma oil alone. With the bases containing polysorbate 60 and POE (4) lauryl ether maximum amounts of ephedrine hydrochloride were dialyzed but essentially no increase was noted with ephedrine. Other minor discrepancies are noted. All surfactant-containing bases with HLB values of less than 9 dialyzed less ephedrine than the base composed only of theobroma oil.

Comparing the dialysis of aminophylline with the dialysis of ephedrine and ephedrine hydrochloride reveals little pattern of consistency. Those bases containing surfactants with HLB values of less than 9 had little effect on the rate of dialysis but surfactants with HLB values of greater than 9 had large increases in the amount dialyzed. This lack of consistency re-emphasizes the necessity for determining the rate of release of each individual drug in each base.

SUMMARY AND CONCLUSIONS

1. The rate of dialysis of aminophylline from various types of suppository bases was determined. Wide variations were found in the amount of aminophylline dialyzed.

2. The effect of the 28 nonionic surfactants added to theobroma oil was variable, although all increased the amount of aminophylline dialyzed. In general, surfactants with low HLB values afforded least increase, and surfactants with HLB values of 11 to 14 showed greatest increase.

3. Those surfactants containing sorbitan in the molecule dialyzed lesser amounts than corresponding surfactants without sorbitan (polyoxyethylene fatty acid esters and polyoxyethylene fatty ethers).

4. It is not clear what effect, if any, the type linkage of the surfactant (*e.g.*, ether, ester, *etc.*) has on the rate of release.

5. It appears that the degree of saturation of the

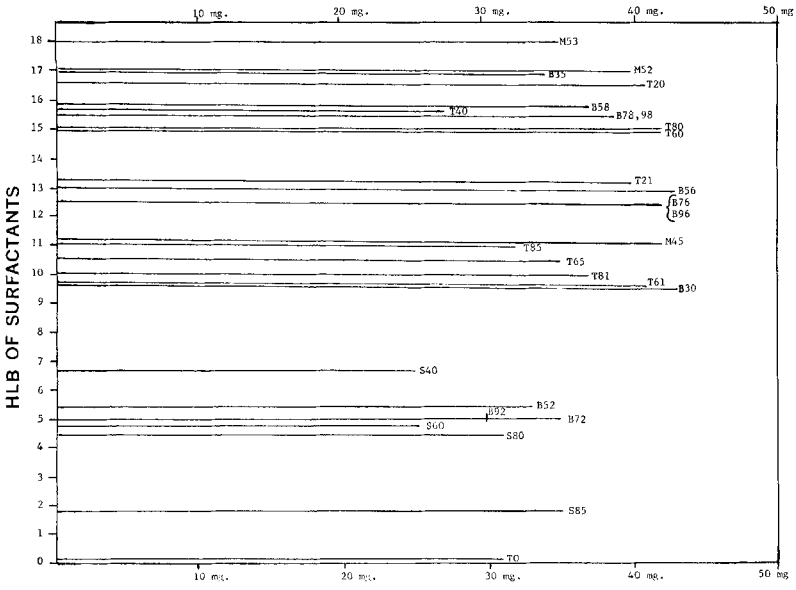

Fig. 2—Milligrams of ephedrine HCl dialyzed after 1 hr. Key same as in Fig. 1.

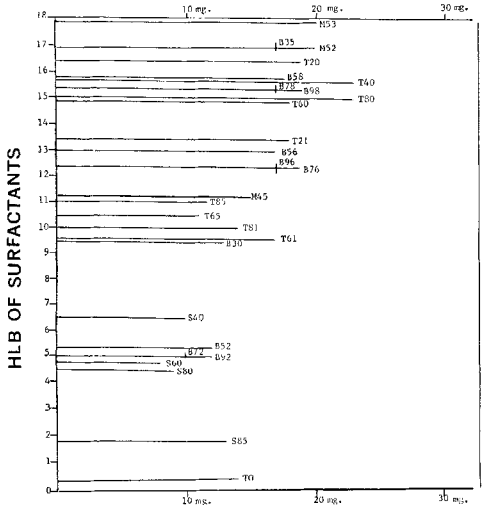

Fig. 3—Milligrams of ephedrine dialyzed after 1 hr. Key same as in Fig. 1.

surfactant, which should affect the melting characteristics of the suppository, has an effect.

6. The rate of dialysis of ephedrine and ephedrine hydrochloride from theobroma oil suppositories containing nonionic surfactants was also determined.

7. For ephedrine hydrochloride no consistent pattern was noted for surfactants having an HLB value of less than 9. Above an HLB value of 9, the surfactants increased moderately the amount of ephedrine hydrochloride dialyzed, but the increases were much less than noted with aminophylline.

8. For ephedrine alkaloid, essentially the same pattern of behavior was noted except that much less drug was liberated and dialyzed in the same period of time. For surfactants with an HLB value of less than 9 there was a decrease in the amount dialyzed.

9. The rate of release of drugs from suppositories containing nonionic surfactants remains unpredictable and should be determined for each drug in each base.

10. This study utilizing a relatively large number of nonionic surfactants points to the possibility of error in using only a small number of surfactants and drawing widespread conclusions.

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