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Diffusion of Benzocaine from Ointment Bases

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Abstract □ The release of benzocaine from oleaginous, absorption, emulsion (water-in-oil and oil-in-water), and water-soluble ointment bases *via* dialysis through a cellulose membrane to an aqueous sink was studied at 37.5°, and benzocaine release from some commercially available products was compared with experimental preparations. The rate of release was found to be greater from water-soluble bases than from other bases and was generally dependent on the concentration of drug in the base. An explanation is offered for the case in which the rate of release is not concentration dependent.

Keyphrases □ Benzocaine—release from various ointment bases, dialysis through cellulose membrane □ Ointment bases—comparison of rate of release of benzocaine, dialysis through cellulose membrane □ Vehicles—diffusion of benzocaine from various ointment bases

It is well recognized that one important function of an ointment base is the control it exerts over the release and, therefore, the therapeutic activity of the medication it carries. For topical preparations, there are two general approaches to the formulation problem of maximizing the absorption of the active ingredient from the vehicle. One approach is to include an agent that affects the barrier function of the epidermis, and the second is to alter the physical characteristics of the vehicle and, thus, the diffusion of the drug from the vehicle to the skin (1). When considering only the second approach, an experimental procedure that measures the release of drug from an ointment base should be of value in determining a base of choice for the formulation of an active ingredient. The methods available for measuring the release of drug from a semisolid were recently reviewed (2). Although some investigators have tried to develop models for the prediction of the relative release rates of a drug from various vehicles, it is generally felt to be impossible (2). Before it can be said that a drug is released best by a specific base, the release rates must be compared by some experimental means.

Local anesthetics have been widely used in therapeutic, diagnostic, and surgical situations because of their ability to inhibit pain and itch sensations by reversibly blocking both generation and conduction of impulses in nervous tissue. These agents have been administered by a variety of routes, but topical application for the relief of pain and pruritis is generally used by the lay public. A significantly large number and variety of these products are readily available for purchase as nonprescription items. Among the categories of products marketed that frequently include a local anesthetic in their formulation are burn and sunburn preparations, hemorrhoidal products, throat sprays and lozenges, eczema and psoriasis remedies, teething lotions, otic products, and topical first-aid preparations. Benzocaine (ethyl *p*-aminobenzoate) is an extensively used local anesthetic and is commercially available in concentrations varying from a declared amount of 0.5 to 20.0%.

An excellent method has been reported to measure the effectiveness of local anesthetics when applied to the intact skin of human subjects (3). Thirty commercially available products and some specially formulated solutions were evaluated with respect to their ability to block the sensation of itch and burning induced by an electrical current. Not all of the commercial products contained benzocaine; but of those that did, only one was found to be effective in obtunding the sensation of itch and burning associated with electrical stimulation of an area burned with UV light.

The purposes of this investigation were to: *(a)* utilize a simple dialysis cell method to compare the ef-

Table I—Composition, Type, and Benzocaine Concentration of Various Ointment Bases

Ointment	Type of Base	Benzocaine, %
A	Oleaginous[a]	20.0
B	Oleaginous	10.0
C	Oleaginous	5.0
D	Absorption[b]	20.0
E	Absorption	10.0
F	Absorption	5.0
G	Emulsion (w/o)[c]	20.0
H	Emulsion (w/o)	10.0
I	Emulsion (w/o)	5.0
J	Emulsion (o/w)[d]	20.0
K	Emulsion (o/w)	10.0
L	Emulsion (o/w)	5.0
M	Water soluble[e]	20.0
N	Water soluble	10.0
O	Water soluble	5.0
P	Water soluble	2.5
Q	Water soluble	1.0
R	Water soluble[f]	20.0
S	Absorption[g]	—[i]
T	Emulsion (o/w)[h]	—[i]
U	Emulsion (w/o)[j]	1.25
V	Emulsion (o/w)[k]	2.0

[a] White petrolatum. [b] Aquaphor, Duke Laboratories, South Norwalk, Conn. [c] Aquaphor–water (1:1). [d] Neobase, Burroughs Wellcome and Co., Research Triangle Park, N.C. [e] Polyethylene glycol ointment USP. [f] Americaine Ointment, Arnar-Stone Laboratories, Mt. Prospect, Ill. [g] Rectal Medicone Ungent, Medicone Co., New York, N.Y. [h] Solarcaine Lotion, Plough, Inc., Memphis, Tenn. [i] Quantitative statement not provided. [j] Burn-A-Lay first aid cream, Kendall Co., Chicago, Ill. [k] Kip Sunburn Windburn Lotion, Rabin-Winters, El Segundo, Calif.

fect of various ointment bases on the rate and amount of drug (benzocaine) released; *(b)* prepare some experimental formulations and compare the release of benzocaine from these products with one previously found effective in humans (3), as well as some other commercially available products; and *(c)* determine the effect on dialysis rate of varying the concentration of benzocaine in an ointment base.

EXPERIMENTAL

Reagents—Ethyl *p*-aminobenzoate (mp 89–91°), *N*-1-naphthylethylenediamine dihydrochloride (mp 185–191°), sodium nitrite (reagent), ammonium sulfamate (practical), barium chloride (reagent), zinc sulfate (reagent), and polyethylene glycols were obtained from a single source[1]. The barium hydroxide and trichloroacetic acid were both reagent grade[2]. The dialysis membrane[3] used was from a single roll and was allowed to hydrate in distilled water for at least 24 hr prior to use.

Equipment and Methodology—Ointments were prepared by fusion or spatulation on a weight/weight basis. All commercial preparations were spatulated immediately prior to use to remove air bubbles and were tightly packed into glass drug reservoirs (3.1 cm deep and 2.4 cm in diameter). For the dialysis experiments, the hydrated membrane was placed over the opening of the drug reservoir in direct contact with the ointment. The surface was rolled gently with a wet stirring rod to smooth it and remove all air from between the ointment and the membrane, which was then secured in place with an O-ring. The dialysis cell was inverted and immersed slightly in 1000 ml of distilled water in a 1000-ml beaker maintained at 37.5 ± 0.5°, being careful to keep the water level below the O-ring. No attempt was made to control the temperature of the diffusion cell or to stir the receiving "sink." From time zero to 2 hr, at 20-min intervals, 5-ml samples were pipeted from the sink and replaced with 5 ml of distilled water at 37.5°. Care was taken to avoid stirring or agitation with the sampling pipet.

[1] J. T. Baker Chemical Co., Phillipsburg, N.J.
[2] Mallinckrodt, St. Louis, Mo.
[3] Cellophane 215 PD-62, E. I. duPont de Nemours and Co., Inc., Wilmington, Del.

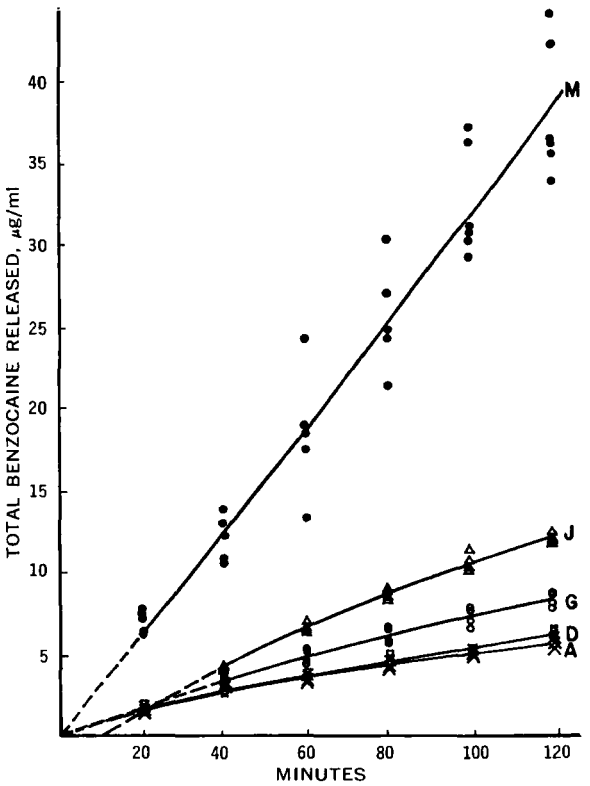

Figure 1—*Effect of ointment base composition on release of drug from preparations containing 20% (w/w) benzocaine. Key: see Table I.*

Analytical Method—The analysis of the benzocaine released during the *in vitro* test was carried out by the method of Matsumoto *et al.* (4). Aliquot portions of a sample solution were diluted appropriately, 5 ml of the dilution was pipeted into a test tube followed by 2 *N* HCl (2 ml) and 0.2% $NaNO_2$ (0.4 ml), and the

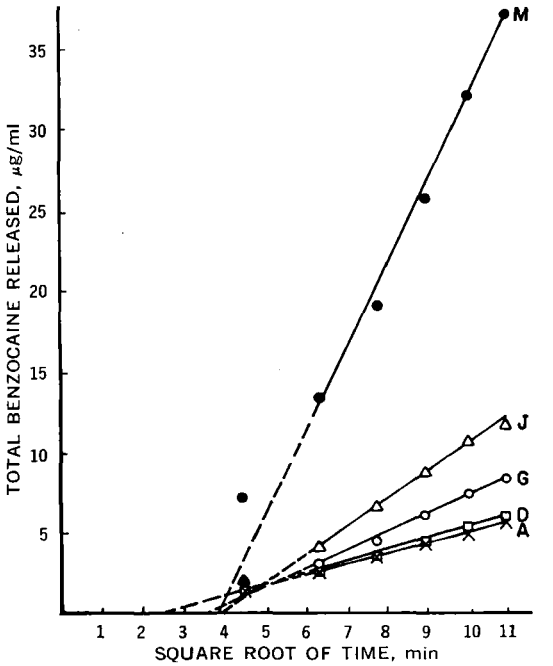

Figure 2—*Correlation between total benzocaine released and square root of time for preparations containing 20% (w/w) benzocaine. Key: see Table I.*

Table II—Summary of Calculated Statistical Parameters: Linear Model

Product	Intercept (b_0)	Standard Error of Intercept	Regression Coefficient (b_1)	Standard Error of Regression Coefficient	Sums of Squares: Regression	Degrees of Freedom: Regression	Sums of Squares: Residual	Degrees of Freedom: Residual
A	−1.368	0.121	0.633	0.015	46.386	1	0.534	22
B	−0.713	0.215	0.430	0.026	42.709	1	7.002	46
C	−0.713	0.103	0.281	0.012	9.127	1	0.383	22
D	−1.657	0.225	0.694	0.027	55.686	1	1.847	22
E	−0.992	0.109	0.472	0.013	5.767	1	0.433	22
F	−0.720	0.069	0.341	0.012	13.450	1	0.335	22
G	−2.786	0.347	1.009	0.042	117.770	1	4.385	22
H	−1.522	0.250	0.663	0.030	50.848	1	2.262	22
I	−1.337	0.156	0.604	0.019	42.175	1	0.886	22
J	−5.666	0.362	1.619	0.043	303.171	1	4.763	22
K	−3.742	0.270	1.207	0.032	168.337	1	2.639	22
L	−2.419	0.150	0.814	0.018	76.597	1	0.816	22
M	−16.881	1.481	5.022	0.177	4373.990	1	184.654	34
N	−38.588	2.779	9.037	0.332	14164.603	1	650.424	34
O	−40.600	3.375	8.882	0.403	20516.553	1	2152.743	51
P	−35.997	4.502	7.381	0.538	9449.051	1	1707.125	34
Q	−17.841	1.473	3.624	0.176	3036.200	1	329.837	46
R	−17.300	2.074	4.915	0.248	4188.757	1	362.245	34
S	−0.197	0.065	0.307	0.008	10.877	1	0.155	22
T	−0.011	0.144	0.292	0.017	9.832	1	0.752	22
U	−0.312	0.048	0.209	0.006	5.027	1	0.085	22
V	−1.077	0.132	0.369	0.016	27.586	1	1.999	40

mixture was shaken for 5 min. Then 0.5% $NH_4SO_3NH_2$ (0.4 ml) was added to this mixture and it was shaken for 3 min. Then 0.5% of *N*-1-naphthylethylenediamine dihydrochloride (1.0 ml) was added with shaking. After 30 min of intermittent shaking, the percent transmittance was measured[4] at 550 nm and the concentration of benzocaine was determined from a standard curve.

The dialysis of the polyethylene glycols was detected turbidimetrically (5). An appropriate volume of sample was diluted to 1.0 ml and added to 10 ml of distilled water. To this was added 1.0 ml of 10% (w/v) anhydrous barium chloride and 2.0 ml of 0.3 *N* barium hydroxide, with swirling after each addition. Next, 2.0 ml of 5% (w/v) zinc sulfate was added, the containers were covered with parafilm, and the mixture was shaken vigorously. After 10 min the contents were filtered[5] and 1.0 ml of the filtrate was mixed with 4 ml of 30% (w/v) trichloroacetic acid containing 5% (w/v) anhydrous barium chloride. All results were read 1 hr after adding the last reagent at 650 nm in a spectrophotometer[4], using the appropriate filter and light source. The amount of dialysis was determined using a standard curve constructed for either polyethylene glycol 400 or polyethylene glycol 4000.

RESULTS AND DISCUSSION

Table I shows the composition of the ointment bases selected to investigate variations in rate of release and dialysis of benzocaine. Since the active ingredient content of many commercial products is reported as a percentage rather than an amount, all products

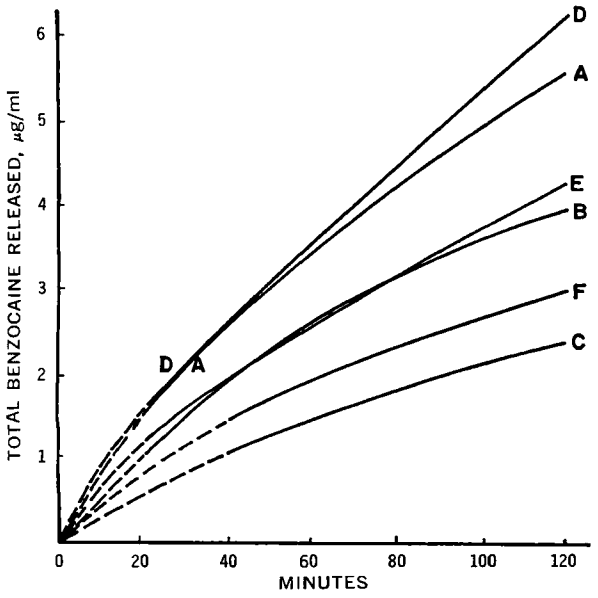

Figure 3—*Effect of varying drug concentration on release of benzocaine from oleaginous and absorption bases. Key: see Table I.*

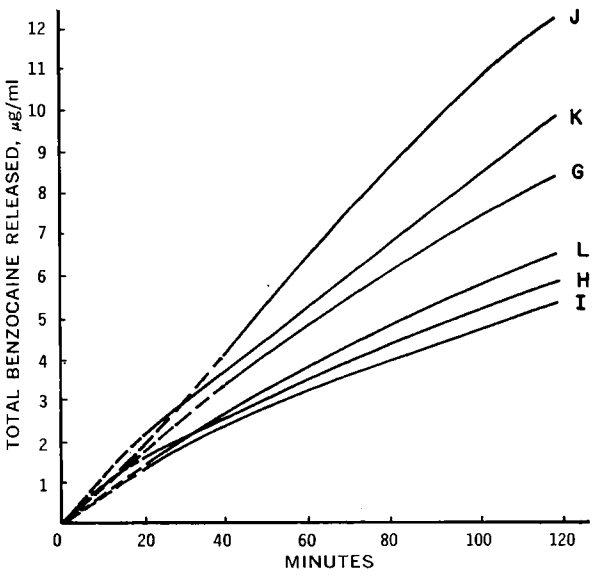

Figure 4—*Effect of varying drug concentration on release of benzocaine from emulsion (oil-in-water and water-in-oil) bases. Key: see Table I.*

[4] Spectronic 20, Bausch and Lomb, Rochester, NY 14602

[5] Whatman No. 42 filter paper, double thickness.

Table III—Individual Comparisons Made

Product	Product[a] V	U	T	S	R	Q	P	O	N	M	L	K	J	I	H	G	F	E	D	C	B	A
A	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	ns	*	*	–
B	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	ns	–	*	–	
C	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	~*	–	–	–		
D	–	–	–	–	–	–	–	–	–	–	–	–	–	ns	ns	*	*	*	–			
E	–	–	–	*	–	–	–	–	–	–	–	–	–	*	*	–	*	–				
F	–	*	–	ns	–	–	–	–	–	–	–	–	–	*	–	–	–					
G	–	–	–	–	–	–	–	–	–	–	–	–	*	*	*	–						
H	–	–	–	–	–	–	–	–	–	–	*	*	–	ns	–							
I	–	*	–	*	–	–	–	–	–	–	*	–	–	–								
J	–	–	–	–	*	*	–	–	–	*	*	*	–									
K	–	–	–	–	–	–	–	–	–	–	*	–										
L	*	–	*	–	–	–	–	–	–	–	–											
M	–	–		–	–	ns	*	*	–	–												
N	–	–	–	–	*	*	ns	ns	–													
O	–	–	–	–	–	*	ns	–														
P	–	–	–	–	*	*	–															
Q	–	–	–	–	*	–																
R	*	*	*	*	–																	
S	–	*	–	–																		
T	~*	–	–																			
U	–	–																				
V	–																					

[a] ns = not significant, ~ * = barely significant, * = significant, and – = not tested for significance.

prepared were made on a percent weight/weight basis. The specific gravity of the bases used varied; therefore, the total benzocaine present also varied for products with different bases but the same concentration of benzocaine.

The penetration of a topically applied drug from an ointment can be modified simply by altering the composition of the vehicle (6). Figure 1 illustrates the variation in drug release from different ointment bases containing the same concentration (w/w) of benzocaine. Individual points are included to show the range of results obtained[6].

The diffusion of drug from semisolids can be described by equations derived for defined physical models. Most models require that the drug alone is allowed to diffuse out of the vehicle. In this experiment, both polyethylene glycol 400 and polyethylene glycol 4000 were found to diffuse through the membrane in the study of benzocaine diffusion from polyethylene glycol ointment USP. Regardless of which physical models are appropriate for the conditions and systems utilized in this study, it was determined that the experimental data were fairly well approximated by a straight line when the amount of drug released was plotted *versus* $t^{1/2}$ for the time period studied. The mean values of at least six determinations for the amount of drug released *versus* $t^{1/2}$ for the products in Fig. 1 are shown in Fig. 2. A least-squares line for the amount of drug released *versus* $t^{1/2}$ was generated for all products in Table I, and the parameters obtained were used to test the null hypothesis that the regression coefficients were identical. A summary of the calculated statistical parameters is given in Table II.

Table III shows the comparisons among rates of benzocaine release from the various semisolid bases as measured by the regression coefficient of the total benzocaine released on the square root of time. It is obvious that all comparisons made are not statistically independent. Therefore, when a comparison is noted as significant at the 95% confidence level, it is meant that the rates of release for the two products under comparison are likely to be different but at a confidence level slightly less than 95%. If the result is noted as "barely significant," then under more rigorous testing the result might not prove to be significantly different. It is true, however, that if regression coefficients were found not to be significantly different, it is highly unlikely that a Type II error was made.

Hydration of skin results from water diffusion from underlying epidermal layers or from perspiration that accumulates after the application of an occlusive vehicle or covering on the surface. Under occlusive conditions, the stratum corneum water content may change from the normal 5–15% to as much as 50% and permeability increases markedly (7). Oleaginous bases are occlusive and might, therefore, be considered desirable as vehicles for topically applied drugs. Figure 3 shows[7] the relative release of benzocaine from two oleaginous vehicles, each containing three different concentrations of drug.

Emulsion bases may exhibit either oleaginous or aqueous properties, depending on whether they are water-in-oil or oil-in-water emulsions, respectively. A survey of the literature concerned with the release of drugs from these vehicles leads to the conclusion that prediction of which base will best release the drug is not possible. The dialysis results utilizing varying concentrations of drug

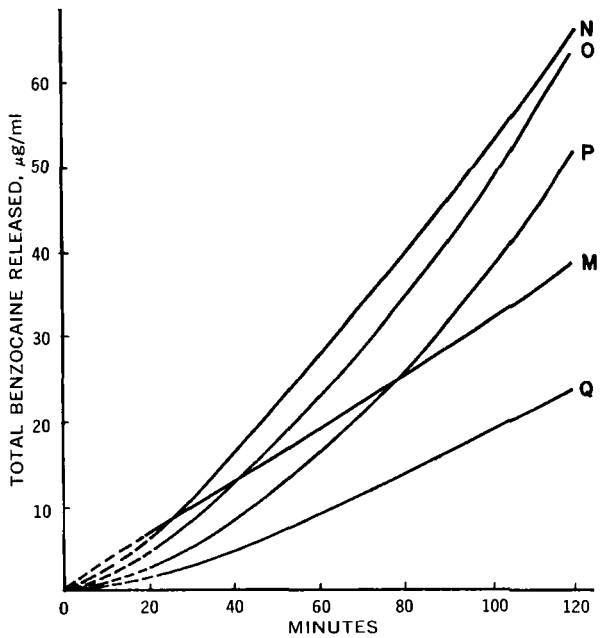

Figure 5—*Effect of varying drug concentration on release of benzocaine from a water-soluble base. Key: see Table I.*

[6] Similar ranges were obtained for all curves in Figs. 3–6 but were not included due to visual indistinguishability.

[7] In Figs. 3–6 the lines shown are those predicted using an iterative curve-fitting procedure and a digital computer. At least four determinations were made at each time, and the line was obtained from the following general equation: $Y = B_1 + B_2e^{B3X}$. Point spread about the lines was similar to that seen in Fig. 1.

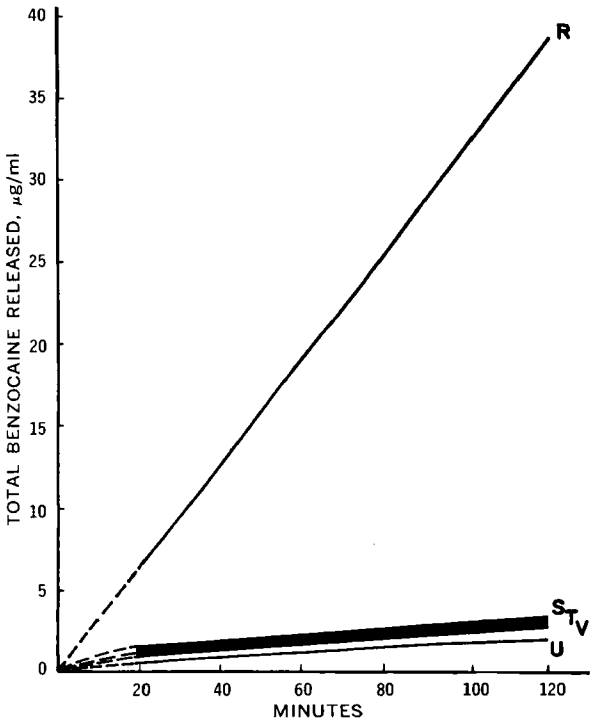

Figure 6—*Release of benzocaine from commercially available products. Key: see Table I.*

in water-in-oil and oil-in-water vehicles are shown in Fig. 4. It can be observed from Figs. 3 and 4 that benzocaine release from the vehicles used follows the same general trend as in Fig. 1 and is concentration dependent.

A general rule in ointment formulation is that if the drug is held firmly by the vehicle, such as when the drug dissolves in the vehicle, the rate of release of the drug will be slow. Conversely, if the drug has a low affinity for the vehicle, it will be readily released (7). Benzocaine is readily soluble in polyethylene glycols and might be predicted to be released quite slowly, at least compared to the other vehicles mentioned, in which benzocaine is not soluble. It can be seen in Fig. 1, however, that the polyethylene glycol vehicle released considerably more drug than any other vehicle. This ready release is further indicated by the curves in Fig. 5, which illustrate the dialysis of five different concentrations of benzocaine from the polyethylene glycol vehicle.

The decreased dialysis of 20% benzocaine in polyethylene glycol vehicle relative to the 2.5, 5.0, and 10% (w/w) preparations was not anticipated, but an interpretation may be offered. During dialysis, a dense, white precipitate formed between the ointment base and the dialysis membrane for the 20% preparation. A lesser amount of precipitate appeared for the 10% preparation and was not observed at all for the 5.0, 2.5, and 1.0% preparations. Water may diffuse through the membrane with formation of a water–polyethylene glycols solution. The precipitate is formed as a result of a marked decrease in solubility of benzocaine in the water–polyethylene glycols solution. A decreased rate of dialysis could be due to the need for an additional dissolution step for those preparations where a precipitate was observed or the precipitate may block the diffusion of the polyethylene glycols–benzocaine solution through the membrane.

Figure 6 shows the results of dialysis of benzocaine through the cellophane membrane from five different commercially available products. Different types of vehicles and varying concentrations of benzocaine are represented. Release studies have long been used as one criterion for judging the possible effect of vehicles on drug availability from topical formulations. There are obvious limitations to such methods, and conclusions must be drawn with great caution. However, the commercial product that gave the greatest release in this experiment gave a greater release than any of the experimental formulations and is the same as the one found effective *in vivo* (3). Furthermore, the relative release rates shown in Fig. 1 correlate with the *in vivo* rectal absorption in rats of radioactivity from benzocaine-^{3}H-containing ointments. These results will be the subject of a future report.

SUMMARY AND CONCLUSIONS

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

2. The ability to release benzocaine for dialysis from ointment bases was found to be: polyethylene glycol > oil-in-water emulsion base > water-in-oil emulsion base > absorption base > white petrolatum.

3. One commercial product was found to release more benzocaine than any other commercial product or any experimental formulation tested.

4. Increasing the concentration of benzocaine in the vehicle caused a corresponding increase in the amount of benzocaine dialyzed through a cellophane membrane with the exception of the polyethylene glycol vehicle. The anomaly is explained in terms of the solubility of the drug and the vehicle.

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