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Absorption and Distribution of Radioactivity from Suppositories Containing ^{3}H-Benzocaine in Rats

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Abstract □ The effects of the suppository vehicle, drug concentration, and nonionic surfactants on *in vitro* benzocaine dialysis through a cellulose membrane and on rectal absorption in rats of total radioactivity following administration of ^{3}H-benzocaine were investigated. *In vitro* dialysis correlated quite well with *in vivo* absorption, and drug release was greater from water-soluble vehicles than from oleaginous vehicles. Inclusion of a nonionic hydrophilic or lipophilic surfactant in cocoa butter resulted in a statistically significant increase for *in vitro* drug release, while a lipophilic surfactant showed little effect *in vivo* and a hydrophilic surfactant depressed release *in vivo*. Both types of surfactant had small effects on release from polyethylene glycol. *In vitro* release of benzocaine from some commercially available suppositories was compared with experimental preparations. Variation in blood radioactivity following administration of the same concentration of ^{3}H-benzocaine in the same dosage form in male and female rats is reported.

Keyphrases □ Absorption—benzocaine from suppositories, effect of vehicle, drug concentration, and nonionic surfactants, rats □ Distribution—benzocaine from suppositories, effect of vehicle, drug concentration, and nonionic surfactants, rats □ Benzocaine—absorption and distribution from suppositories, rats □ Suppositories—absorption and distribution of benzocaine, rats □ Dosage forms—suppositories, absorption and distribution of benzocaine, rats

It is well recognized that formulation factors can influence the availability of a drug from a dosage form. Surface-active agents included in dosage forms may exert their effects on the active ingredient, the dosage form itself, or the membrane at the absorption site. Surfactants have been reported to increase and to decrease the absorption of drugs (1). Moreover, varying the concentrations of a surfactant can enhance or retard drug absorption, depending on the type of surfactant and whether or not micelle formation occurs (1).

The complex mechanisms of surfactant effects on drug absorption were reviewed previously (2). The *in vitro* release of benzocaine from ointment vehicles was reported (3) and compared (4) to the rate of absorption and resulting total blood level radioactivity following rectal administration of 20% ^{3}H-benzocaine (ethyl *p*-aminobenzoate) from ointment vehicles in rats. This paper reports the effects of suppository vehicles, variations in drug concentration, and the presence of a nonionic hydrophilic or lipophilic surfactant on the *in vitro* dialysis of benzocaine and the absorption of ^{3}H-benzocaine in rats.

EXPERIMENTAL

Dosage Form Preparation—All suppositories were prepared by the fusion method, and commercial products were used as received. The reagents and equipment used were similar to those reported previously (3, 4). Additional materials used in the present experiment were: dialysis membrane, available as a 2.54-cm (1-in.) × 30.5-m (100-ft) roll[1]; cocoa butter[2]; polysorbate 80[3]; and sorbitan monooleate[4].

For *in vivo* studies, ^{3}H-benzocaine was dissolved in the polyethylene glycol vehicle (75% polyethylene glycol 1000 and 25% polyethylene glycol 4000) or suspended in the cocoa butter vehicle. Suppository vehicles containing ^{3}H-benzocaine were poured into plastic, disposable, U-80 insulin syringes, which were refrigerated until completely congealed. The tips of the syringes were cut off, and the excess semisolid was removed.

A suppository volume of 0.5 ml was used for the experiment. The amount of surfactant used was too small to weigh directly, and the aliquot method was used for preparation.

***In Vitro* Dialysis**—Dialysis tubing was cut into 10-cm lengths and soaked for at least 24 hr in distilled water. At the time of the test, the tubing was closed and weighted at one end by tying with a thin strip of the dialysis tubing to a glass stopper. The suppository was introduced into the tubing followed by 2.5 ml of distilled water. The top was tied to form a container, which was as nearly full as possible without loss of water.

The sample was then placed in a 600-ml beaker containing 500 ml of distilled water maintained at 37.5°. It floated upward, being held near the center of the container by the glass stopper weight. At the appropriate time periods, 5-ml samples were pipetted from the beaker and 5 ml of distilled water (37.5°) was returned to the beaker. Care was taken to draw each sample from as close to the same place in the beaker as possible and to avoid stirring.

Analytical Method—The analysis of the benzocaine released during the *in vitro* test was carried out by the method of Matsumoto *et al.* (5). Aliquot portions of a sample solution were pipetted into a test tube followed by 2 *N* HCl (2 ml) and 0.2% $NaNO_2$ (0.4 ml), and the mixture was shaken for 5 min. Then 0.5% $NH_4SO_3NH_2$ (0.4 ml) was added, and the mixture was shaken for 3 min. *N*-(2-Diethylaminoethyl)-1-naphthylamine hydrochloride (1.0 ml of 0.5%) was then added with shaking.

After 30 min of intermittent shaking, the percent transmittance was measured at 550 nm and the concentration of benzocaine was determined from a standard curve.

***In Vivo* Studies**—Female Sprague–Dawley rats were used for all experiments except the male *versus* female study. Animal weights varied between 100 and 280 g. Surgical preparation, cannulation,

[1] Seamless regenerated cellulose dialysis tubing, Catalog No. 25225-226, VWR Scientific Supplies, Portland, Ore.
[2] Hershey Food Corp., Hershey, Pa.
[3] Tween 80, J. T. Baker, Phillipsburg, N.J.
[4] Span 80, J. T. Baker, Phillipsburg, N.J.

Table I—Composition and Benzocaine Concentration of Various Types of Suppository Bases

Suppository	Vehicle	Surfactant	Average Weight for Dialysis Study[a], g	Benzocaine, %	Total Benzocaine for Dialysis, mg	Total Benzocaine Dialyzed in 5 hr, mg	Percent Dialyzed in 5 hr	Average Weight for *In Vivo* Release[b], g	Total ^{3}H-Benzocaine Available for *In Vivo* Release, mg
A	Polyethylene glycol[c]	None	—	20	—	—	—	0.579	115.8
B	Polyethylene glycol	None	2.35	10	235.0	80.5	34.3	0.573	57.3
C	Polyethylene glycol	None	—	5	—	—	—	0.567	28.4
D	Polyethylene glycol	None	2.41	3	72.3	57.0	78.8	0.569	17.1
E	Polyethylene glycol	Sorbitan monooleate, 1%	2.42	3	72.6	60.5	83.3	0.558	16.7
F	Polyethylene glycol	Sorbitan monooleate, 0.5%	2.42	3	72.6	45.8	63.0	0.554	16.6
G	Polyethylene glycol	Polysorbate 80, 1%	2.41	3	72.3	57.8	79.9	0.552	16.6
H	Polyethylene glycol	Polysorbate 80, 0.05%	2.33	3	69.9	55.5	79.4	0.556	16.7
I	Polyethylene glycol	None	—	1	—	—	—	0.581	5.8
J	Cocoa butter	None	—	20	—	—	—	0.510	102.0
K	Cocoa butter[d]	None	1.63	10	163.0	22.9	14.0	0.510	51.0
L	Cocoa butter	None	1.74	3	53.2	10.0	18.8	0.475	14.2
M	Cocoa butter	Sorbitan monooleate, 1%	1.77	3	53.1	11.9	22.4	0.438	13.1
N	Cocoa butter	Sorbitan monooleate, 0.05%	1.76	3	52.8	12.4	23.5	0.443	13.3
O	Cocoa butter	Polysorbate 80, 1%	1.67	3	50.1	13.9	27.6	0.468	14.0
P	Cocoa butter	Polysorbate 80, 0.05%	1.60	3	48.0	11.7	24.4	0.460	13.8
Q	Oleaginous[e,f]	Unknown	2.14	11	235.0	17.5	7.5	—	—
R	Cocoa butter[e,g]	Unknown	2.65	4.9	130.0	15.5	12.0	—	—
S	Cocoa butter[e,h]	Unknown	2.40	5.4	130.0	13.2	10.1	—	—

[a] Average weight of 10 suppositories. [b] Average weight of six or more suppositories. [c] Polyethylene glycol vehicle consisted of polyethylene glycol 1000 (75%) and polyethylene glycol 4000 (25%). [d] Hershey's. [e] Commercially available product. [f] Also contains hexachlorophene, ephedrine sulfate, and bismuth subgallate. [g] Also contains oxyquinoline sulfate, zinc oxide, menthol, and balsam peru. [h] Also contains ephedrine sulfate, oxyquinoline sulfate, zinc oxide, bismuth subgallate, and balsam peru.

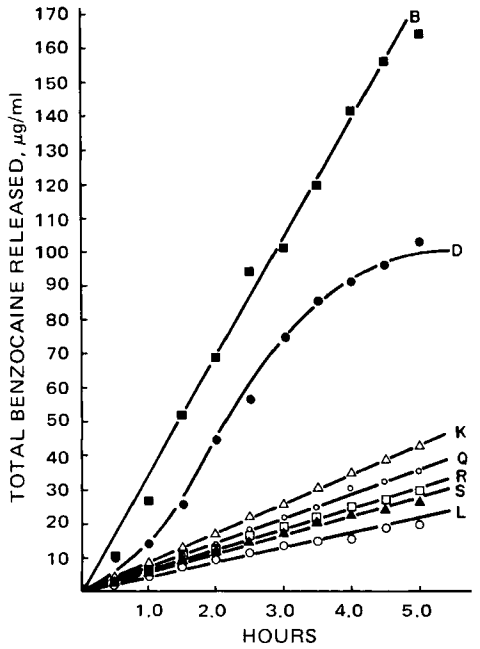

Figure 1—*Effect of suppository vehicle composition on release of drug from preparations containing benzocaine. Key: see Table I.*

blood sample collection, and blood analysis methodology were followed as previously reported (4).

RESULTS AND DISCUSSION

Table I shows the composition of suppositories selected for the investigation of variations in dialysis and rate of release for absorption of benzocaine. Figure 1 illustrates the variation in drug release of some experimental suppository formulations and the commercial products investigated. Since the active ingredient content of many commercial products is reported as a percentage, rather than an amount, Products A–P were prepared on a percentage weight per weight basis. The specific gravity of the polyethylene glycol vehicle used was about 1.4

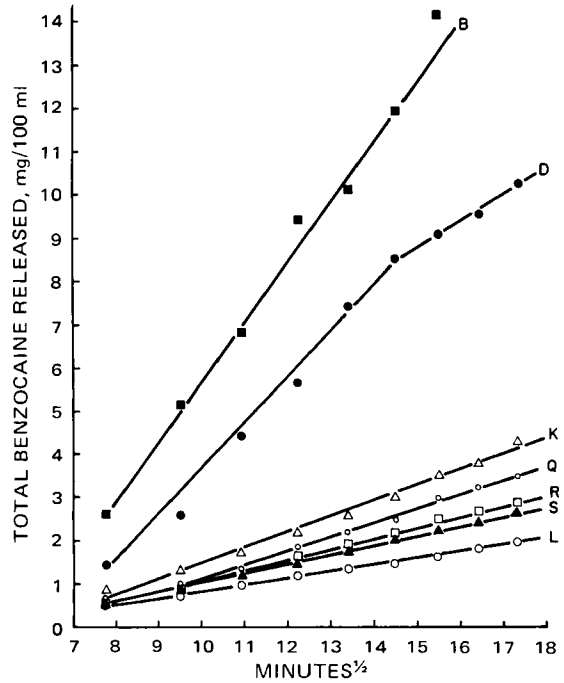

Figure 2—*Relationship between total mass of drug dialyzed and time$^{1/2}$. Key: see Table I.*

Table II—Summary of Calculated Statistical Parameters

Product	Intercept (b_0)	*SE* of Intercept	Regression Coefficient (b_1)	*SE* of Regression Coefficient
B	−88.9583	4.2313	113.5101	2.4429
D	−62.6965	7.3624	76.0611	4.2507
E	−90.9342	8.1531	96.8973	4.5225
F	−69.2085	5.8930	74.6488	3.2689
G	−76.7483	5.5375	87.5097	3.0717
H	−81.1662	4.4574	86.9697	2.4725
K	−21.1737	1.3366	27.8889	0.7717
L	−6.8433	0.5277	11.6569	0.3047
M	−8.5915	0.3772	14.3776	0.2178
N	−10.7434	0.5166	15.6600	0.2982
O	−10.6500	1.3357	17.8333	0.7712
P	−8.6347	0.6929	14.5876	0.4001
Q	−18.4070	1.0351	23.6619	0.5976
R	−11.9034	0.5641	16.9296	0.3257
S	−13.0224	0.8578	18.6843	0.4952

times that of the cocoa butter, and this difference was reflected in the variation in the total amount of benzocaine present in suppositories containing the same percent of benzocaine but different vehicles.

The total mass of drug transferred from semisolids under the conditions of the *in vitro* experiment was nearly linear with respect to the square root of time for the times investigated (Fig. 2). The linear portions of such benzocaine release curves were used in generating a linear least-squares regression line, and comparisons among the estimated parameters (Table II) were made (Table III) using the usual null hypothesis. The data points for Product D were approximated with two linear portions (Fig. 2), and the line for the early time period was arbitrarily chosen for statistical comparisons (Tables II and III).

In vitro testing of suppositories involves many considerations and some compromises in simulating conditions operating during rectal absorption. The conditions (6) that should be emulated are: (*a*) an average temperature of 36.9°; (*b*) water not present in the liquid state but present in the semisolid feces, which are 77–82% water; (*c*) rectal mucosa acting as a semipermeable membrane, allowing passage of water both away from and into the blood, depending on the osmotic gradient; (*d*) practically no peristaltic movement; (*e*) pressure on rectal contents varying from 0 to 50 cm of water, according to posture; and (*f*) possible presence of feces.

In normal people, fecal material is present in the rectum just prior to defecation only (7). Most of the time, this organ is free of solid matter which could physically interfere with absorption. Therefore, it is not necessary to introduce a material for *in vitro* testing that would simulate the presence of feces. It is necessary, however, to expose the dosage form to some fluid so that the drug has an opportunity to dissolve. While this exposure may seem to violate Condition *b*, a positive correlation between *in vitro* testing and *in vivo* results would indicate that such exposure to fluids is acceptable for testing purposes.

Testing at body temperature is critical, especially for products that melt in the rectum. Conditions *a* and *c* are readily satisfied by using a temperature-controlled water bath and placing the suppository inside a commercially available, semipermeable, dialysis membrane tubing. Condition *d* can be met by placing the dosage form in an unstirred medium. Although this procedure may allow a buildup of drug around the dosage form, which can slow drug release, such a static dialysis method may have a closer relationship to the absorption of drugs through a biological membrane than dialysis when the bulk phase is stirred.

The data reported here were obtained using a simple dialysis procedure, without stirring of the bulk receptor phase, which exposed the suppositories tested to a single, uniform pressure and approximated to some degree Conditions *a*, *c*, and *d*.

Examination of the results for the commercial products (Fig. 1) reveals less release from the 11% preparation than the 10% preparation and somewhat greater release from the 4.9% preparation than the 5.4% preparation, although the latter difference is not significant. Formulation factors other than concentration that could be playing a role include the presence of other ingredients that might interact with the benzocaine as well as different vehicle effects. The experimental cocoa butter formulations were completely melted within 10 min and the polyethylene glycol vehicles were dissolved within 1 hr. There was, however, no visible change in any commercial product during the 5-hr dialysis period. Each commercial suppository retained its shape, al-

Table III—Individual Comparisons Made[a]

Products	S	R	Q	P	O	N	M	L	K	H	G	F	E	D	B
B	—	—	*	—	—	—	—	—	*	*	*	*	*	*	—
D	—	—	—	—	—	—	—	*	*	ns	ns	ns	*	—	
E	—	—	—	—	—	—	*	—	—	—	ns	*	—		
F	—	—	—	—	—	*	*	—	—	~*	—	—			
G	—	—	—	—	*	—	—	—	—	ns	—				
H	—	—	—	*	—	—	—	—	—	—					
K	—	—	*	*	*	*	*	*	—						
L	*	*	—	*	*	*	*	—							
M	*	*	*	—	*	*	—								
N	*	ns	*	~*	—	—									
O	ns	ns	*	*	—										
P	*	*	*	—											
Q	*	*	—												
R	ns	—													
S	—														

[a] Comparisons among rates of benzocaine release from the semisolid as measured by the regression coefficient of the total benzocaine released with respect to the square root of time were made. All of these comparisons 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 of benzocaine for the two products under comparison are likely to be different but at a confidence level slightly less than 95%. The result is that some of the differences in release rate noted as ~* might not prove to be significantly different under more rigorous testing; ns = not significant, ~* = barely significant, * = significant, and — = not tested for significance.

though they all became somewhat more pliable at the end of the experiment than at the beginning.

The dialysis of drug from saturated benzocaine solutions was studied, and the ratio of total benzocaine to free benzocaine increased proportionately as the concentration of a nonionic hydrophilic surfactant[3] was increased from 0 to 7%. Addition of the surfactant to a solution containing a fixed amount of benzocaine increased the dialysis rate compared to a solution without surfactant (5, 8). Therefore, 0.05 and 1.0% of sorbitan monooleate or polysorbate 80 were incorporated into both the polyethylene glycol and the cocoa butter vehicle containing 3% benzocaine.

Figure 3 shows the effect on the cocoa butter suppositories and the increase in the amount and rate of benzocaine released. The greatest increase in release was due to the presence of 1% polysorbate 80. Since the membrane was not controlling the rate of diffusion (as evidenced by increasing diffusion with an increased concentration), the surfactant must have been increasing the rate of dissolution of the drug. This finding is consistent with work showing that an increase in benzocaine dialysis from surfactant-containing solutions is due to the increased solubilization of the drug because of surfactant–drug interactions, followed by a rapid release of free drug as dialysis takes place (5, 8).

Figure 4 shows the results of dialysis from polyethylene glycol suppositories containing surfactants. Between 63 and 80% of the active ingredient was released (Table I).

It is not possible to use the actual amount of drug released from the different products (Table I) as a measure of the effect of the vehicle on dialysis of drug, since the amount present varies with the product considered. The percent of drug released, however, can be used for this purpose. The total released from the polyethylene glycol vehicle containing 10% benzocaine was almost 2.5 times the total released from the corresponding cocoa butter preparation when the percent benzocaine dialyzed was considered. The ratio was 2.9 to 4.2 when comparing the corresponding preparations containing 3% benzocaine. When considering the release from the 3 *versus* 10% preparations of a single vehicle type, it can be seen that the 10% formulation released a larger amount of drug but a smaller percent of drug during the dialysis period (Table I).

Various concentrations of ^{3}H-benzocaine in suppository dosage forms with and without surfactant (Table I) were selected for *in vivo* testing and were inserted into the rectum of female Sprague–Dawley rats. Blood samples (0.1 ml) were taken from the inferior vena cava at 5, 10, 20, 30, 40, 60, 90, 120, 180, 240, and 300 min, and the total

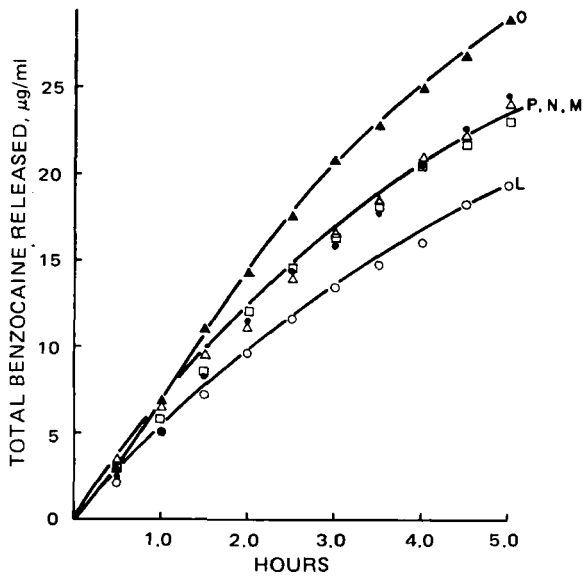

Figure 3—*Effect of surfactants on drug release from cocoa butter suppositories. Key: see Table I.*

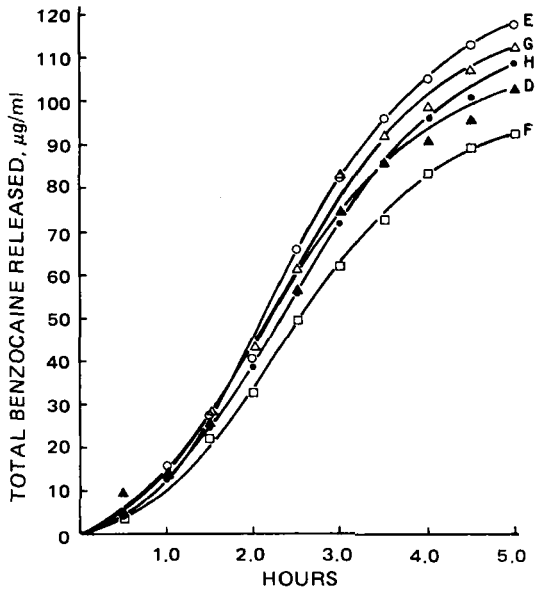

Figure 4—*Effect of surfactants on drug release from polyethylene glycol suppositories. Key: see Table I.*

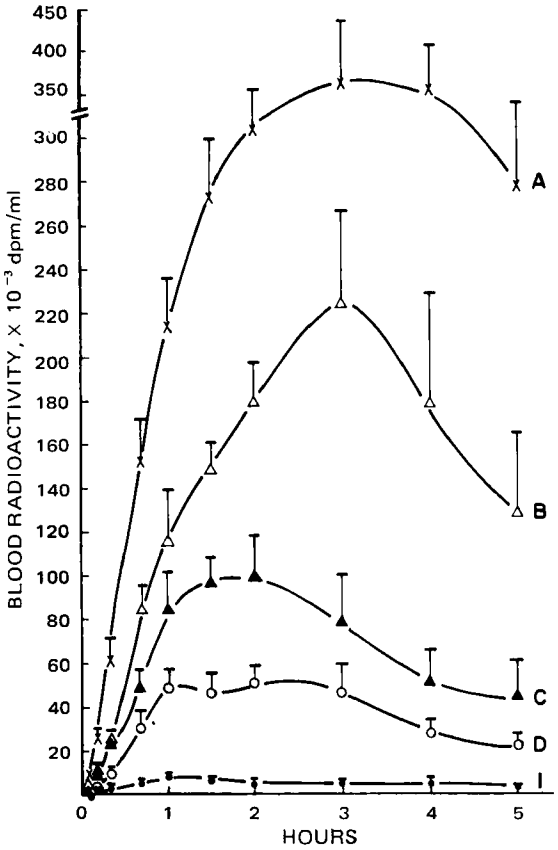

Figure 5—*Blood radioactivity after the application of ^{3}H-benzocaine in a polyethylene glycol suppository vehicle. Key: see Table I. A* t*-value larger than the critical* t*-value was obtained for all point comparisons except curve I* versus *B at 5 and 10 min; curve C* versus *B at 5, 10, 20, and 300 min; and curve B* versus *A at 180 min. (One side of the standard error of the mean is shown.)*

radioactivity present was determined. The means of the radioactivity detected are shown in Figs. 5–9.

Statistical analysis using unequal variance techniques indicated that weight variation among animals accounted for less than 5% of the variation following different dosage formulations. The standard error of the mean is included in some figures but not in others due to crowding. A point-by-point comparison of the means obtained at each sample time for the nonlinear curves was made using the Student *t* test (95% confidence level), and the results are summarized in the figure legends.

Due to the relatively large dispersion of experimental values, the ability to distinguish between mean values, which appear quite distinct, is compromised. An example of this situation can be seen when comparing the results from Formulation A *versus* Formulation B in Fig. 5 for the 180-min sample. The mean values for A and B were significantly different for each sample time (95% confidence level) except at 180 min due to the relatively large variances at that time. Increasing the number of animals in the study may have resulted in a significant difference in this case.

The blood level radioactivities from different concentrations of ^{3}H-benzocaine in polyethylene glycol suppositories (1, 3, 5, 10, and 20%) and cocoa butter suppositories (3, 10, and 20%) are shown in Figs. 5 and 6. Increasing the concentration of ^{3}H-benzocaine in both polyethylene glycol and cocoa butter suppository bases resulted in a higher total radioactivity in the blood. Since the volume of suppositories was equal with every concentration of drug administered, the total dose was increased by increasing the drug concentration. Both concentration and variation in total dose may be causes for the difference in the shape of the blood level curves using the same suppository vehicle.

It is clear from Fig. 5 that an increase in the ^{3}H-benzocaine in polyethylene glycol increased the area under the curve up to 5 hr. Although this finding indicates an increase in the amount of drug being absorbed from the rectum, since the drug had to be absorbed

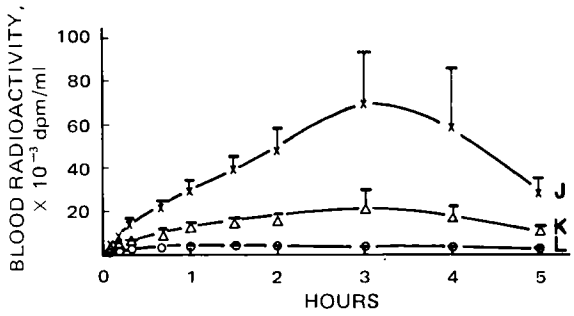

Figure 6—*Blood radioactivity after the application of ^{3}H-benzocaine in a cocoa butter suppository vehicle. Key: see Table I. A* t*-value larger than the critical* t*-value was obtained for all point comparisons except curve L* versus *K at 180 min, curve L* versus *J at 240 min, and curve K* versus *J at 180 and 240 min. (One side of the standard error of the mean is shown.)*

for the radioactivity to appear, under the conditions of this experiment the total radioactivity represents several metabolites rather than intact drug (4). Therefore, no pharmacokinetic analysis using the blood level radioactivity *versus* time curves was done in the present experiment.

A previous *in vitro* study (3) found that an increased concentration of benzocaine in polyethylene glycol ointment caused a decrease in release through a dialysis membrane. That decrease was explained on the basis of a decreased solubility and precipitation of the benzocaine in a polyethylene glycol–water solution, which formed under the *in vitro* conditions. This effect was not observed during the current dialysis experiments and is apparently not occurring *in vivo*, as evidenced by increasing absorption from an increased concentration of drug in this water-soluble vehicle.

The absorption from a cocoa butter suspension of drug is much less in rate and amount when compared to equal concentrations of drug in polyethylene glycol (Fig. 6). The latter vehicle is water soluble and can dissolve in the rectum. Benzocaine was dissolved in the polyethylene glycol vehicle and, therefore, was available to partition into the rectal fluids and the rectal mucosa during liquefaction (dissolution) of the polyethylene glycol. Cocoa butter does not dissolve but melts in the rectum.

Before liquefaction, dissolution of drug in rectal fluids is limited to the drug located at the surface of the suppository. Diffusion through the semisolid suppository is probably of little importance, since melting occurs readily at body temperature. After liquefaction, the

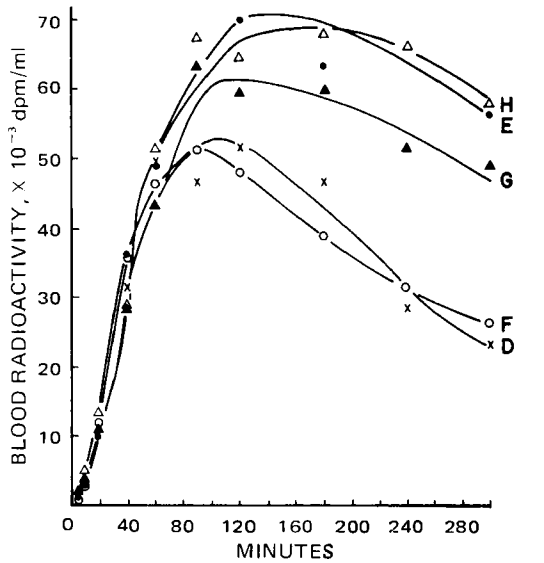

Figure 7—*Blood radioactivity after the application of 3% ^{3}H-benzocaine and surfactants in a polyethylene glycol vehicle. Key: see Table I. A* t*-value larger than the critical* t*-value was only obtained for point comparisons on curve D* versus *E after 240 min, curve D* versus *G after 240 min, curve E* versus *F after 240 min, and curve F* versus *H at 90 min.*

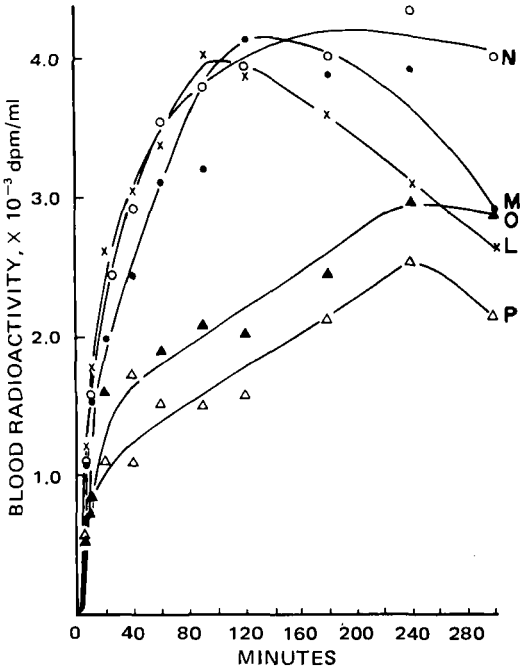

Figure 8—*Blood radioactivity after the application of 3% ^{3}H-benzocaine and surfactants in a cocoa butter suppository vehicle. Key: see Table I. A t-value larger than the critical t-value was found for at least half of the points when comparing the curves of L* versus *O, L* versus *P, M* versus *P, N* versus *O, and N* versus *P.*

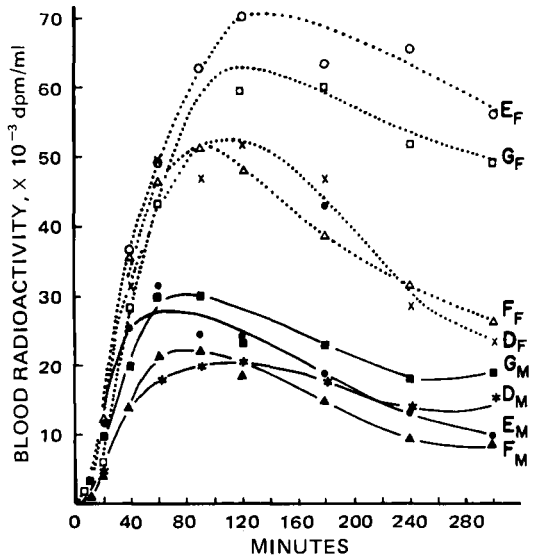

Figure 9—*Comparison of blood radioactivity following 3% ^{3}H-benzocaine in a polyethylene glycol vehicle in male and female rats. Key: see Table I. A t-value larger than the critical t-value was found for point comparisons of male* versus *female rats receiving the same formulation except for the first 60 min for E_F* versus *E_M and G_F* versus *G_M. (The F subscript is for female rats, and the M subscript is for male rats.)*

suspended drug would be coated with melted cocoa butter, which is much less viscous than the original semisolid.

Some drug may be exposed to the rectal fluids for rapid dissolution, but most drug would still have an oleaginous coating in which the drug has a very low solubility. The drug would have to diffuse through this coating before absorption could occur. Therefore, the slower drug absorption from the cocoa butter is not surprising, since the drug particles would be coated by a hydrophobic substance in which the drug has a low solubility.

Surfactants were included in the 3% ^{3}H-benzocaine in polyethylene glycol and cocoa butter suppositories to determine if the presence of a nonionic hydrophilic or lipophilic surfactant would affect the rate or amount of benzocaine absorption. Incorporation of a 1% lipophilic or 0.05 or 1% hydrophilic surfactant in the polyethylene glycol vehicle resulted in an apparent increase in total blood radioactivity (Fig. 7) for times beyond 180 min, although the range of values was wide enough for the differences of the means to be not statistically significant at most times.

With 3% ^{3}H-benzocaine in cocoa butter base, the lipophilic surfactant in both concentrations studied (1 and 0.05%) showed no significant influence on the amount absorbed (Fig. 8). However, the hydrophilic surfactant in both concentrations studied decreased the total counts in the blood significantly with most times under investigation.

Table III shows that for the products in Fig. 4 the release rates of only Formulations D and E were significantly different *in vitro*. All products were essentially the same *in vivo* with respect to the rate of drug release. All products with surfactant in cocoa butter, however, demonstrated a significant increase in the rate of drug release *in vitro*, but the only significant effect *in vivo* was a decrease in release with 1% polysorbate 80. In some cases the *in vitro* method did not accurately predict the *in vivo* effect. In these cases there were relatively small actual differences for the *in vitro* system, although the differences were statistically significant.

In the earlier part of the study, some experiments were run to measure the blood level concentration of radioactivity *versus* time using male rats. Female rats showed a total radioactivity in the blood about twice that of male rats (Fig. 9) when the same dosage form was administered. These differences could be due to differences in the rate of absorption, biotransformation, distribution, or excretion. Absorption across rectal membranes is usually considered to be a passive diffusion process. In passive diffusion, either the release of drug from the vehicle or drug dissolution in rectal fluids would be the rate-limiting step for absorption, especially with a drug like benzocaine which has a low water solubility.

The decreased rate of appearance of radioactivity in the blood from 20% ^{3}H-benzocaine in the cocoa butter vehicle compared to 20% ^{3}H-benzocaine in polyethylene glycol indicates that the rate of absorption is dependent on the amount of drug released from the vehicle and presented to the rectal mucosa, at least for the concentrations of drug studied here. Since the same vehicle and drug concentration were administered to males and females, it is unlikely that the observed differences were due to differences in absorption. Furthermore, the differences probably were not due to differences in excretion half-life of the parent drug or of identical amounts of the same metabolites in males or females because most drugs are excreted by a first-order process in either sex.

Excretion of total radioactivity and loss from the bloodstream may be different in males and females if metabolism is occurring at different rates and if different amounts of metabolites are available for excretion. One possible explanation for the results could be that males were metabolizing the drug to more polar products faster than the females and the more polar products were being cleared from the bloodstream more rapidly than the parent drug. Another possible explanation could be that distribution of the molecules containing radioactivity was different for male and female rats. Further work involving tissue distribution and metabolism is underway in these laboratories to determine which possibility is correct.

SUMMARY AND CONCLUSIONS

A simple dialysis method was used to measure the release of benzocaine from various experimental and commercially available suppositories. Wide variations were found in the amount of benzocaine dialyzed. Small differences, which were detectable *in vitro*, were not seen *in vivo* in rats, although substantial differences *in vitro* were correlated well with experimental results obtained *in vivo*.

Benzocaine was dialyzed and absorbed rectally in rats more rapidly from a polyethylene glycol vehicle than from cocoa butter, and the effects of the surfactants tested were variable. Rectal administration of the same concentration of ^{3}H-benzocaine in the same vehicle to male and female rats results in lower blood radioactivity *versus* time curves for the male rats.

Some formulation factor other than the concentration of benzocaine affected the relative amounts of benzocaine released *in vitro* from the commercially available products examined. Although the dialysis method is useful for evaluating the effects of formulation on drug

release from suppositories, the desirable release rate for the specific drug investigated has not been determined since its minimum effective concentration is not known. Considerably more research is needed in this area.

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Attainment of Highly Uniform Solid Drug Dispersions Employing Molecular Scale Drug Entrapment in Polymeric Latices

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Abstract □ The uniformity of distribution attainable for an amine drug in solid dispersions prepared using a molecular scale entrapment procedure was investigated. Excellent reproducibility of drug content throughout the entire entrapment product was demonstrated in both flocculated (high drug levels) and deflocculated (low drug levels) systems. Drug content and content uniformity were found to be predictable for deflocculated systems, even at high drug dilution ratios. Milling or particle-size fractionation appeared to have no effect on the distribution of drug throughout the solid dispersion entrapment products. Dry blending was inferior to molecular scale drug entrapment in distributing small quantities of drug uniformly.

Keyphrases □ Dispersions, solid—amine drugs, uniformity of distribution, molecular scale entrapment procedure, flocculated and deflocculated systems □ Molecular scale drug entrapment—utilized to prepare solid dispersions of amine drugs, uniformity of distribution studied □ Distribution uniformity—amine drugs in solid dispersions studied, molecular scale entrapment procedure, effect of milling or particle-size fractionation □ Amine drugs—uniformity of distribution in solid dispersions, molecular scale drug entrapment procedure

Safety, efficacy, and reliability are the three basic criteria that define the quality of any well-designed pharmaceutical dosage form. High standards of drug product quality are necessary for the protection of the public, and one important facet of quality assurance is the maintenance of content uniformity. Content uniformity directly bears on each of the three criteria defining drug product quality. The importance of content uniformity in solid unit dosage forms to the consumer's health, safety, and welfare becomes obvious when one considers the potency of many drugs in use today.

BACKGROUND

Failure to meet content uniformity specifications in a solid dosage form may be attributed to weight variation between dosage units or improper mixing (nonhomogeneity of drug distribution). Another factor resulting in inaccuracies of drug content in tablets, capsules, or powders is drug segregation. Improper mixing leading to nonuniformity can result from the inherent difficulty in setting the "ideal mixing time" for high dilution solid dosage forms. Homogeneity of a potent active ingredient throughout a powder mix is highly dependent on particle size and shape, particle-size distribution, density, moisture, and charge. Furthermore, the size, efficiency, and type of mixer can make a difference when choosing a mixing time specification.

A "perfect mix" for a powder formulation would be exemplified by a three-dimensional location of drug plus excipient in space, in which every drug particle is the same size and is the same distance in all planes from every other drug particle. Two miscible liquids most closely approach (in practice) a perfect mix, since mixing occurs at a molecular level and is completely random. This result is never attained in powder blending due to the finite number of particles involved and the factors previously listed that may contribute to unmixing or segregation. However, a reasonable mix is possible if there are enough particles per drug dose and if the optimum mixing time is selected after carrying out adequate testing and sampling of the powder blend.

A high degree of mixedness achieved in a powder mix, however, does not necessarily mean the final product will meet content uniformity specifications. Segregation can occur when the mix is removed from the mixer, transferred to another point in the plant, or subsequently treated by other processing procedures. Furthermore, for capsules and tablets, nonuniform flow and subsequent weight variation could hinder unit-to-unit drug content even more.

In addition to these manufacturing problems, other problems concerning the control of content uniformity include analytical methods and statistical procedures. To allow content uniformity determinations on individual unit dosage forms, the assay methods must be accurate, reliable, and specific as well as sufficiently sensi-