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INFLUENCE OF DIELECTRIC CONSTANT OF THE BASE ON THE RELEASE OF ACETAMINOPHEN FROM SUPPOSITORIES

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ABSTRACT

The dielectric constant of various polyethylene glycol suppository bases (vehicles) was investigated in relation to the release of acetaminophen as measured by dissolution. Bioavailability of the drug from the bases was also studied in the rectum of beagle dogs. Blood samples were removed at appropriate time intervals and the acetaminophen analyzed by an improved GLC method. A solubility study of acetaminophen in dioxane-water mixtures indicated that maximum solubility of the drug occured at a dielectric constant of about 14. The bioavailability results in dogs showed minimum release of drug in bases of dielectric constants near 14 and increased release characteristics in bases farther removed from this dielectric constant. The results suggest that vehicles with lower solubility for the drug tend be release acetaminophen readily and provide improved bioavailability.

INTRODUCTION

The importance of the rate of release of a drug from a suppository base has been long recognized (1-9). Considerable research has been devoted to a study of the factors affecting the release of a drug from a suppository base. Factors such as the drug entity, the physiological environment, the suppository base and the patient may influence the bioavailability of a drug dosage form (10-15). In addition, physiochemical factors are significant in the design of suppositories with improved bioavailability. Martin, et al. (16-18), have applied the Hildebrand treatment (19) to study the influence of solvents on solubility. Paruta, et al. (20-25), used dielectric constant to study the solubility of drugs in various solvents. Pagay, et al. (1) investigated the influence of dielectric properties on the bioavailability of drugs from polyethylene glycol suppository bases. The purpose of this investigation is the application of these concepts in the design of an acetaminophen suppository with improved bioavailability. The procedure involves measuring the solubility characteristics of acetaminophen as a function of dielectric constant, then the dielectric constant of a variety of potential suppository bases is determined. Finally, the minimum in the solubility versus dielectric constant curve is matched with the base of a combination of bases having the selected dielectric requirement. Further, an in vitro dissolution test has been developed which demonstrates the invluence of the suppository base on drug release. This test was used successfully to screen potential suppository formulations and was correlated to acetaminophen plasma levels in dogs.

MATERIALS AND METHODS

Solubility Measurements:

Acetaminophen N. F. (S. B. Penick, Lot #7032-LRR-61). No pretreatment was considered necessary and was used directly. Freshly deionized water and dioxane (Mallinekrodt's Scintillar Grade, Lot BER) wer the solvents used. Deionized distilled water was used to prepare binary mixtures with dioxane. Ten ml of solvents containing dioxane-water in 10% increments were added to 20 ml screw-capped Teflon-lined test tubes. An excess of acetaminophen of approximately 4 g was added to each test tube. The test tubes were labelled, placed on a Dubnoff metabolic shaker and the bath temperature maintained at 25°C ± 0.2°C. Equilibrium solubility was attained in 24 hours. After equilibration, the test tubes were centrifuged at 2000 rpm's for 10 minutes. Appropriate samples were obtained for immediate spectrophotometric analysis. The concentration of acetaminophen was determined from absorbance at 240 nm and previously determined Beer's Law plots.

Dielectric Measurements:

An E. H. Sargent Model V Oscillometer with inductance compensator was set up with the large cell holder in a small, forced draft, hot air oven. Standards (acetone, O-dichlorobenzene, chlorobenzene, chloroform and benzene) were measured at 25°C for calibration of the instrument. Samples were prepared by completely melting the total sample in a one liter beaker, stirring and transferring approximately 250 ml to a 250 ml beaker. The beakers, with samples were placed in a 55 or 60° C oven with the cell holder for four hours to allow for temperature equilibration. The cell was cleaned between each sample by washing with water, rinsing twice with acetone, and then dried with a hot air blower. Approximately 5 to 10 minutes after introduction of temperature equilibrated samples into the cell, a zero check was made and then readings were taken.

Measurements in the solid state were attempted but were unsuccessful due to the solid suppository bases contracting from the sides of the cell. This led to erratic and nonreproducible results.

Dissolution Studies:

A covered, 1000 ml glass beaker (26); a variable speed motor, model 163 (Hanson Research Corporation, Northridge, California); a cylindrical stainless stell USP basket (26) fabricated from type 316 stainless steel; and a water bath (Chicago and Electric Co., Catalog No. 1300) were used for the dissolution studies.

Five hundred ml of freshly deionized water was put in the beaker and allowed to heat to 37°C. The shaft of the motor with the USP basket containing the suppository were lowered to 2 cm from the bottom of the beaker and the motor run at 50 rpm. Aliquots were withdrawn at appropriate intervals of time and replaced immediately with a corresponding volume of deionized water to maintain a constant volume of 500 ml. Proper dilution of each sample was made for spectrophotometric analysis. Acetaminophen concentration was determination from the absorbance and previously determined Beer's Law plots at 240 nm.

Bioavailability Studies:

Five mature, healthy beagle dogs obtained from Marshall Research Animals were used in the study. The animals were labelled 16518, 15944, 15986, 15943 and 16354. The average body weight was 12.2 Kg (range 10.5 - 13.5 Kg).

The dogs were allowed free access to water until the time of the experiment. The animals were fasted for 24 hours and a 4 oz Fleet enema administered to each animal three hours prior to drug administration. At the time of the experiment the animals were kept in metabolic cages. The suppository was inserted as far into the rectum as possible making sure that the suppository was past the anal sphincter. All dogs retained the suppositories. For blood sampling, a total of 10 ml blood samples were collected by routine venipuncture over a 3 hour period according to the following schedule: 0, 1, 1.5, 2 and 3 hours after administration. After completion of the study, the dogs were released from the metabolic cages to return to their normal cages.

The blood was centrifuges at 3000-4000 rpm's for 15 minutes. Plasma specimens were drawn off by use of a Pasteur pipette. Care was taken to avoid the collection of red blood cells along with the plasma. Plasma specimens were frozen until assayed.

Analysis of Acetaminophen in Plasma:

An improved procedure for the GLC determination of acetaminophen (N-acetyl-p-aminophenol) in the presence of N-butyryl-p-aminophenol (internal standard) was employed. The method is based on the extraction of acetaminophen from plasma with ethyl acetate containing a known amount of N-butyryl-p-aminophenol. Following a clean-up step with a basic buffer solution and neutralization with acid, both compounds are re-extracted into ethyl acetate. The ethyl acetate is evaporated to dryness and the residue dissolved in 5 µl of pyridine and 15 µl of acetic anhydride at 42°C. One to two µl samples are injected directly into the gas chromatography. The detailed analysis has been reported elsewhere (30).

RESULTS AND DISCUSSION

The observed solubility of acetaminophen as a function of the composition of dioxane-water mixures is illustrated in Table 1. The data shows that equilibrium solubility is reached within 24 hours. In addition, solubility maximum occurs between 20 and 30 volume percent of water. This corresponds to a range in dielectric constants of 10.7 and 17.7. Previous measurements by Paruta (27) have shown a maximum in solubility to occur at the same position. However, the results presented in Table 1 show higher values than those of Paruta in the range of 50% or less of water. At levels of water in excess of 50%, the agreement between the two sets of data is good. These differences in the solubility profile could possibly be attributed to the quality of dioxane used.

TABLE 1

Solubility Profile of Acetaminophen in Dioxane-Water Mixtures.

		Concentration mg/ml		
% Water	Dielectric Constant	24 hours	48 hours	average of columns 3 & 4
0	2.2	28.0	27.0	28.0
10	5.6	235.0	231.0	233.0
20	10.7	284.0	284.0	284.0
30	17.7	280.0	277.0	279.0
40	25.9	244.0	249.0	247.0
50	34.3	207.0	199.0	203.0
60	43.0	141.0	139.0	140.0
70	51.9	89.0	92.0	90.0
80	60.8	51.0	51.0	51.0
90	69.7	28.0	25.0	26.0
100	78.5	14.0	11.0	13.0

The effect of dielectric constant on the formulation of acetominophen suppositories is postulated to be as follows. If the rate limiting step is the release of acetaminophen from the suppository base, a base which dissolves the drug to maximum extent will not readily release the drug for bioavailability. Conversely, a base with a dielectric constant that does not provide high solubility for acetaminophen may lead to a more bioavailable formulation. Examination of Table 2 and Figure 1 shows that the rate of release of the drug from the suppository base decreases as the dielectric constant of the base increases.

TABLE 2

Batch	Suppository Base	Measurement Temperature	Dielectric Constant	% Acetaminophen Dissolved in 20 minutes
8	PEG 1000	60°C	6.86	78
	PEG 1540	60°C	8.84	
	PEG 4000	60°C	8.46	
	PEG 6000	60°C	8.01	
H	75% PEG 1000 25% PEG 4000	53°C	8.61	63
	50% PEG 1000 50% PEG 4000	60°C	7.56	
	25% PEG 1000 75% PEG 4000	60°C	8.03	
	10% PEG 1000 90% PEG 4000	60°C	8.17	
	30% PEG 1540 70% PEG 6000	55°C	8.48	
	40% PEG 1450 60% PEG 6000	60°C	8.49	
310	30% PEG 1450 50% PEG 6000 20% H_2O	60°C	16.1	42
S	Batch S	55°C	13.53 - 17.36	45

Raw and normalized plasma levels of acetaminophen in dogs are shown in Table 3. This Table includes the method of normalization which was necessary due to differences in body weight between dogs, and in the different dose of acetaminophen administered to the animals. The graphical representation of the normalized acetaminophen

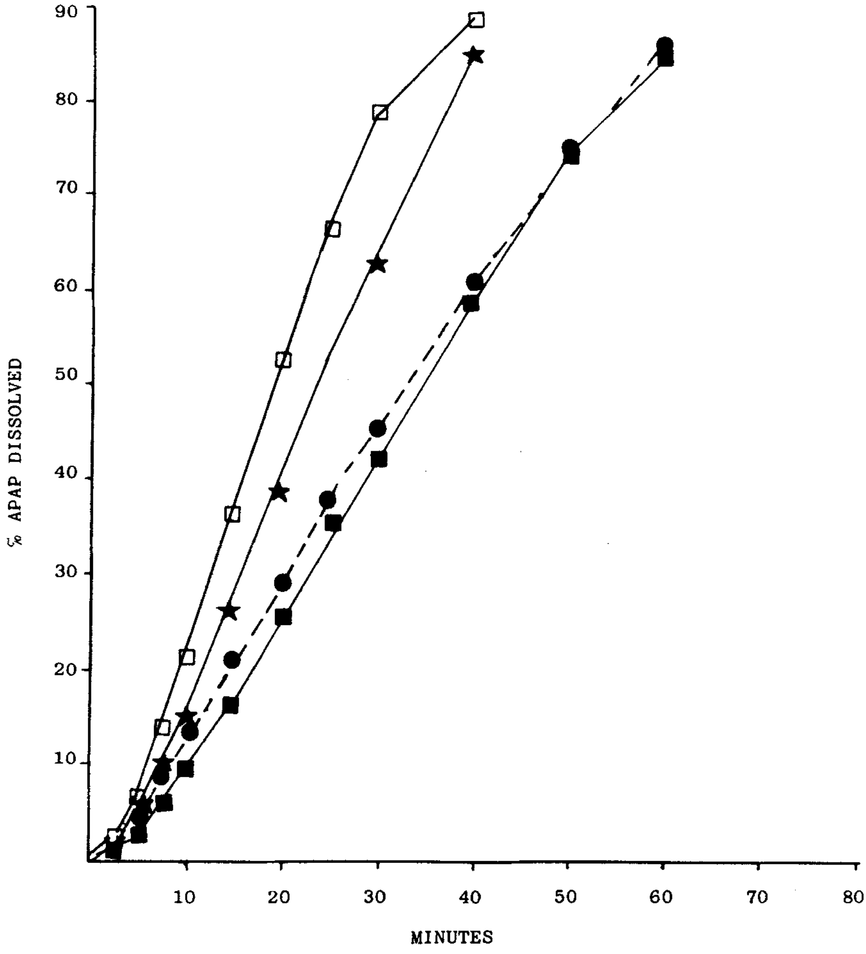

FIGURE 1: In Vitro dissolution profile of acetaminophen suppositories.
□ Batch 8, ★Batch H, ● Batch S, and ■ Batch 310

plasma levels is shown in Figure 2. The data tends to support the trend observed in the *in vitro* dissolution studies. The formulations containing low molecular weight PEG's (1000 to 4000) show better plasma level profiles (batches H and 8) than batch S which contains

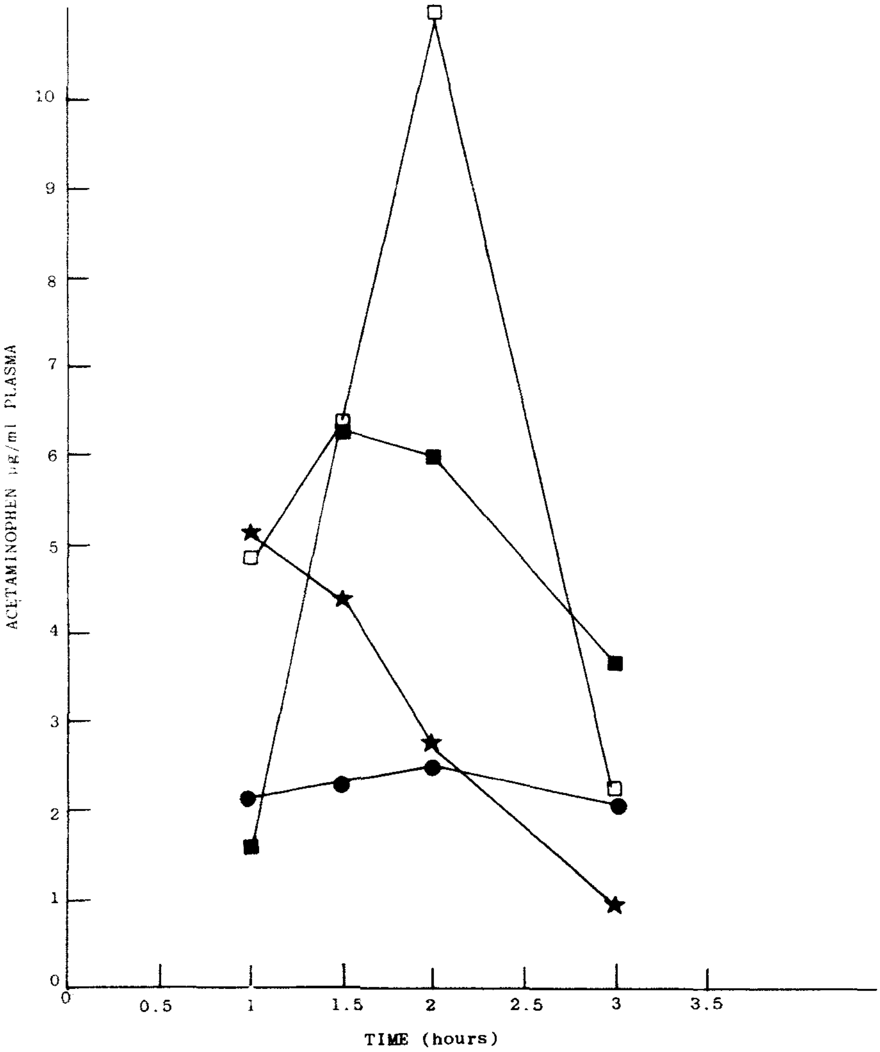

FIGURE 2: Normalized acetaminophen plasma levels in dogs after rectal administration of ☐ Batch 8, ★ Batch H, ● Batch S, and ■ Batch 310.

high molecular weight PEG's (4000-6000). These results indicate an apparent correlation between the *in vitro* dissolution studies and the *in vivo* rectal absorption studies. However, further studies are

TABLE 3

Summary of *In Vivo* Acetaminophen Suppository Studies in Dogs.

Time	Acetaminophen Concentration (µg/ml)			
	Batch X	Batch H	Batch 8	Batch S
0	0	0	0	0
1	1.67	4.19	3.38	1.65
1.5	6.29	3.54	4.38	1.74
2.0	6.04	2.23	7.59	1.90
3.0	3.67	0.79	1.53	1.59
Dog Number	16518	15986	15943	16354
Body Weight (Kg)	10.5	11.5	13.5	12.5
Acetaminophen Dose in mg.	376.0	334.0	334.0	339.0
Dose in mg/Kg Body Weight	35.81	29.04	24.81	27.12

(continued. . .)

required to establish a more accurate correlation using a greater number of animals. If this correlation is achieved, it might be possible to use the *in vitro* dissolution studies as an indicator of *in vivo* bioavailability.

Batch "X" which is Weecobee M formulation (water-insoluble base) shows a profile comparable to the low molecular weight PEG formulations. The trend of the data indicates that suppositories which do not satisfy high solubility requirements for acetaminophen may release the drug more readily and lead to better bioavailability.

TABLE 3 - Continued

Normalized Plasma Levels*

Time	Batch X	Batch H	Batch 8	Batch S
0	0	0	0	0
1	1.67	5.17	4.88	2.18
1.5	6.29	4.37	6.32	2.30
2.0	6.04	2.75	10.96	2.51
3.0	3.67	0.97	2.21	2.10

* The data was normalized using the following expression:

$$C_p^n = C_p \cdot d/D_o = C_p \cdot 35.81/D_o$$

Where, C_p^n is the normalized acetaminophen plasma level. D_o is the acetaminophen dose in mg/Kg body weight at time zero, and d is the dose of batch "X" in mg/Kg body weight. The dose Batch "X" is taken as 35.81 mg/Kg. This normalization assumes that the plasma level is directly proportional to the dose. It also takes into consideration body weight and dose administrated to the animal.

In summary, the results of the present investigation corroborate the work of previous investigators (1, 28, 29) who have suggested a relationship between the dielectric properties of the suppository vehicle and rectal absorption of drugs. The *in vitro* dissolution method used in the present study, which appears to correlate with rectal absorption studies in dogs, will be compared in future work to plasma level data from humans. At the present time it appears that in vitro dissolution methodology and dielectric measurement of suppository bases serve as excellent guides in the development of suppository formulations.

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