Influence of Vehicle Dielectric Properties on Acetaminophen Bioavailability from Polyethylene Glycol Suppositories

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Abstract □ The rectal absorption of acetaminophen from an aqueous solution and from several polyethylene glycol base dosage forms was studied in six human subjects using urinary excretion measurements. A relationship was observed between acetaminophen bioavailability and the dielectric properties of the vehicles utilized. The *in vitro* dissolution rates of acetaminophen in these dosage forms were also studied and were somewhat related to the time of occurrence of the maximum urinary excretion rate.

Keyphrases □ Acetaminophen absorption from polyethylene glycol suppositories—effect of vehicle dielectric properties □ Absorption, acetaminophen from polyethylene glycol suppositories—effect of vehicle dielectric properties □ Polyethylene glycol dielectric properties—effect on acetaminophen absorption from suppositories □ Suppositories, acetaminophen—effect of polyethylene glycol vehicle dielectric properties on drug absorption □ Bioavailability, acetaminophen from polyethylene glycol suppositories—effect of vehicle dielectric properties □ Dielectric properties of polyethylene glycols—effect on acetaminophen absorption from suppositories

The importance of drug release from suppository bases has been recognized by several workers (1–3) who attempted to identify the physicochemical properties of drugs and bases that most greatly influence rectal absorption. Lowenthal and Borzelleca (4) measured plasma salicylate levels following rectal administration of salicylic acid and sodium salicylate in dogs and found that the free acid and its salt were equally well absorbed from cocoa butter suppositories. However, with water-miscible bases, salicylic acid gave higher plasma levels. The effect of formulation variables on the rectal absorption of salicylates was studied (5) and compared to the rectal and oral routes of administration. Based upon urinary salicylate excretion data, both aspirin and sodium salicylate were found to be equally bioavailable from the oral and rectal routes. Aspirin was released more rapidly from water-miscible bases, such as polyethylene glycol and polyoxyethylene (4) sorbitan monostearate with glyceryl monolaurate, than from oily bases. It was found that cocoa butter gave a more rapid release of sodium salicylate, and it was concluded that water-soluble sodium salicylate was more readily released from a suppository base than was the slightly soluble aspirin.

The effect of water-soluble bases on the rectal absorption of several sulfonamides also was reported (6). These bases caused a reduction in the absorption rate of sulfonamides which was shown to depend on the partitioning behavior of the drug between lipid and water-soluble materials. These differences were related to the dielectric constants of the bases. The absorption rate constants for sulfonamides, when released from several water-miscible bases, were correlated with the reciprocal of the dielectric constants of these bases. Thus, from these studies, it appears that water-soluble bases tend to decrease the polarity of the aqueous phase which decreases the partitioning into the lipoidal membrane.

Shangraw and Walkling (7) studied the effect of vehicle dielectric properties on the rectal absorption of acetaminophen in humans. Using urinary excretion measurements, they reported rectal absorption from a microcrystalline cellulose–carboxymethylcellulose gel, a propylene glycol suspension, and a cocoa butter suppository. The cumulative amount of acetaminophen excreted over 6 hr was about the same when the drug was given in the gel and in the cocoa butter suppository and significantly greater than with the propylene glycol suspension. These authors concluded that propylene glycol, having dielectric properties favoring high solubility, retains more drug in the vehicle and causes reduced rectal absorption as compared to either cocoa butter or aqueous gel bases, which have dielectric properties yielding extremely low solubility in the vehicle and subsequently show a higher drug absorption.

It appears that the release of drugs and subsequently their absorption from rectal dosage forms are somewhat related to their solubility in the base, which in turn is related to the respective dielectric properties of the drug and the base. The purposes of this study were: (*a*) to determine the bioavailability of acetaminophen from rectal dosage forms using several polyethylene glycol bases having varying dielectric properties and an aqueous solution; and (*b*) to determine the effects of the dielectric properties of the bases on bioavailability more quantitatively.

EXPERIMENTAL

Dosage Form Preparation—The rectal suppositories were prepared by the fusion method. Each suppository weighed an average of 2.3 g and contained 0.130 g of acetaminophen[1]. The suppositories were assayed for acetaminophen content, which was within ±3% of the specified dose. The bases were polyethylene glycols[1] whose average molecular weights were 400, 1000, 4000, and 6000. The polyethylene glycol 400 formulation was prepared as a 2.3-g liquid. A 5-ml aqueous solution containing 0.130 g of acetaminophen was also utilized.

Bioavailability Studies—Six healthy male subjects, 24–34 years old and 60–85 kg, were employed. Participants were required to observe a normal diet, follow normal sleep habits, drink plenty of water, and abstain from any alcoholic beverages and other drugs during the 24 hr preceding rectal administration of acetaminophen. Upon arising, the subjects ingested 180 ml of water and evacuated the bowel. The bladder was voided, and the urine was collected to serve as a blank specimen. For each study, the subjects inserted one suppository into the rectum. The polyethylene glycol 400 formulation and the aqueous solution of acetaminophen were administered through a rectal tube[2] attached to a calibrated 5-ml plastic hypodermic syringe[3].

[1] Ruger Chemical Co., Hillside, NJ 07205
[2] Davol Inc., Providence, RI 02901
[3] Becton, Dickinson, and Co., Rutherford, NJ 07070

Table I—Mean Rate of Acetaminophen Excretion (Milligrams per Hour ± Standard Error) from Various Formulations in Six Human Subjects

Collection Interval, hr	Formulations				
	Polyethylene Gycol 400	Polyethylene Glycol 1000	Polyethylene Glycol 4000	Polyethylene Glycol 6000	Aqueous Solution
0–1	1.6 ± 0.51	1.4 ± 0.43	1.3 ± 0.29	1.6 ± 0.41	7.7 ± 1.25
1–2	3.7 ± 0.21	3.7 ± 0.29	3.9 ± 0.96	5.5 ± 0.90	12.9 ± 1.05
2–3	6.0 ± 0.29	7.9 ± 0.81	8.4 ± 1.12	8.6 ± 0.69	13.0 ± 0.58
3–4	8.3 ± 1.34	9.8 ± 1.13	8.6 ± 0.67	10.2 ± 0.58	11.5 ± 1.12
4–5	7.6 ± 1.15	7.9 ± 1.31	9.4 ± 0.77	10.8 ± 1.03	9.5 ± 0.27
5–6	6.3 ± 0.78	6.6 ± 0.52	9.2 ± 0.65	8.6 ± 0.89	7.6 ± 0.54
6–7	5.6 ± 1.05	6.6 ± 1.19	6.7 ± 0.54	7.8 ± 0.82	5.7 ± 0.95
7–8	4.4 ± 0.42	4.1 ± 0.56	5.9 ± 0.66	6.8 ± 0.42	4.1 ± 0.71
8–9	4.0 ± 0.52	4.1 ± 0.49	5.1 ± 0.49	5.1 ± 0.26	3.2 ± 0.52
9–10	3.2 ± 0.43	2.7 ± 0.22	4.3 ± 0.33	3.9 ± 0.20	2.2 ± 0.33

After drug administration, the subjects collected complete voids every hour for 10 hr and then pooled all voids up to 24 hr. During the first 10 hr, the subjects were instructed to ingest 180 ml of water after each collection. A normal lunch and supper were eaten immediately following the 4- and 10-hr collections, respectively.

Initially, only the four polyethylene glycol formulations were tested in four subjects. Each subject followed a different treatment sequence to balance any possible sequential effects. The remaining subjects participated at a later time and followed separate sequences. All six subjects were administered the aqueous solution as their last formulation.

Analytical—Acetaminophen content in the suppositories was determined by the method described in NF XIII (8). This method was modified slightly by using aqueous instead of hydroalcoholic solutions. The samples for the dissolution rate measurements were also analyzed by the same procedure.

Acetaminophen and its metabolites were assayed using a literature procedure (9, 10). The analytical procedure involves acid hydrolysis of acetaminophen and its metabolites present in urine to *p*-aminophenol, which reacts with phenol in the presence of ammonia and sodium hypochlorite to form an indophenol dye, which has a spectrophotometric absorbance maximum at 625 nm[4].

Dissolution Studies—The suppositories were tested for the rate at which the drug in the dosage form dissolved, using a slightly modified "beaker method" (11) in which a stainless steel holder was used to maintain the suppository in a vertical position at the bottom of a 100-ml beaker. Eighty milliliters of distilled water was used as the dissolution medium and was maintained at 37°. A four-blade, stainless steel stirrer was used to stir the fluid at 25 rpm. One-milliliter samples were withdrawn at appropriate intervals and assayed to obtain a dissolution profile.

Dielectric Constants—The dielectric constants of all vehicles were determined on a chemical oscillometer[5]. The dielectric cell was calibrated by measuring instrument readings for several organic solvents whose dielectric constants are accurately reported in the literature. The dielectric constants for the polyethylene glycol vehicles were evaluated from a calibration plot of instrument readings *versus* the reported dielectric constants of the standards employed. For those polyethylene glycol vehicles that solidify at room temperature, the material was melted and the liquid was poured in the dielectric cell to the top. After the polyethylene glycol base solidified and equilibrated to room temperature, the dielectric constant was measured.

RESULTS

The mean rates of excretion of acetaminophen for six subjects for all formulations are summarized in Table I. The standard error is listed with each mean value.

The peak or maximum rates of excretion of acetaminophen occurred at 3 hr when the drug was given rectally in solution. The peak excretion rates with polyethylene glycols 400 and 1000 occurred at 4 hr, while the peak rate occurred at 5 hr with the polyethylene glycol 4000 and 6000 formulations. The initial rates of excretion (first 3 hr) were much higher from the aqueous solution than from any of the polyethylene glycol formulations. An analysis of variance performed on the rates for each of the first 3 hr indicated that there were indeed significant differences due to changes in the formulations (F at 1st hr = 16.66; df = 4, 25; $p < 0.01$. F at 2nd hr = 29.60; df = 4, 25; $p < 0.01$. F at 3rd hr = 10.90; df = 4, 25; $p < 0.01$). Moreover, the magnitude of the peak rate of excretion for the aqueous solution was larger than those of most polyethylene glycol formulations. Although polyethylene glycol 6000 showed a longer time to achieve peak excretion than the other polyethylene glycol bases, the rate at this time, 10.797 mg/hr, was greater than the others, even than those exhibiting earlier peak times.

Figure 1 shows the mean cumulative amount of acetaminophen excreted as a function of time following rectal administration of various formulations. There was a fairly wide variation in the total amount of drug excreted after 24 hr following drug administration in the various formulations. The greatest amount of drug was recovered when it was administered rectally in an aqueous solution, followed by the various polyethylene glycol formulations.

Table II shows the results of an analysis of variance of the cumulative excretion of acetaminophen from 1 to 24 hr following rectal administration of acetaminophen in various formulations to

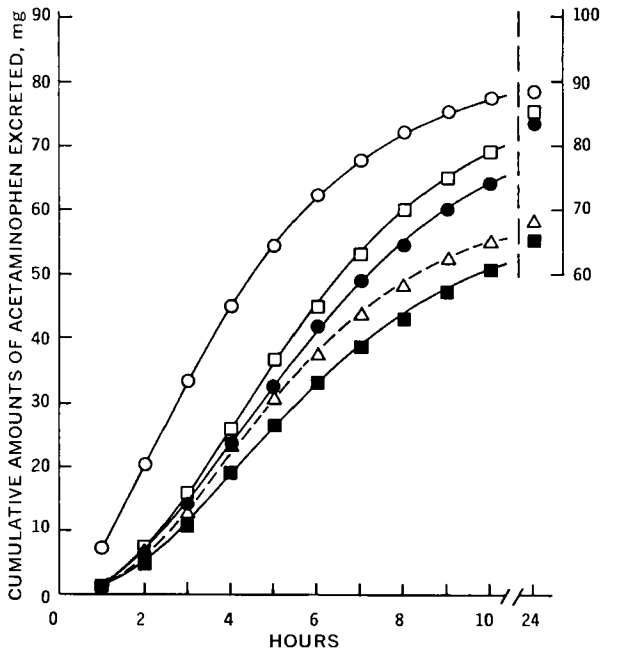

Figure 1—*Effects of various vehicles on the mean cumulative amounts of acetaminophen excreted for six subjects during the 24 hr following rectal administration. Key:* ○, *aqueous solution;* □, *polyethylene glycol 6000;* ●, *polyethylene glycol 4000;* △, *polyethylene glycol 1000; and* ■, *polyethylene glycol 400.*

[4] Beckman model DB-G, Beckman Instruments, Fullerton, CA 92634
[5] Model V, Sargent-Welch Scientific Co., Skokie, IL 60076

Table II—Results of Statistical Analysis of the Cumulative Excretion of Acetaminophen at Hourly Intervals to 10 hr and Total Excretion Values for Studies Involving All Formulations and Those Involving Only Polyethylene Glycol Bases

Hours	All Formulations		Polyethylene Glycol Formulations	
	F^a	p	F^b	p
1	16.66	<0.01	0.12	>0.05
2	27.31	<0.01	0.94	>0.05
3	27.25	<0.01	1.52	>0.05
4	20.83	<0.01	2.10	>0.05
5	17.10	<0.01	3.14	<0.05
6	17.35	<0.01	4.83	<0.05
7	14.42	<0.01	4.47	<0.05
8	12.77	<0.01	5.20	<0.01
9	10.90	<0.01	5.15	<0.01
10	10.05	<0.01	5.51	<0.01
24	8.48	<0.01	8.05	<0.01

[a] Degrees of freedom (4, 25). [b] Degrees of freedom (3, 20).

the same group of subjects. The results revealed significant differences at the 99% level in acetaminophen excretion at all intervals. These differences were due to formulation differences and not to variation among subjects. An analysis of variance was also performed to test differences among only the polyethylene glycol bases (Table II). The results revealed that statistically significant differences in cumulative amounts of acetaminophen excretion occurred at all time periods after 4 hr. These differences were the result of differences among the various formulations and not of variations among the subjects.

Figure 2 shows the rate of dissolution of acetaminophen in terms of the percent of drug undissolved as a function of time from rectal suppositories containing polyethylene glycol 1000, 4000, and 6000. Each dissolution profile represents an average of three determinations. Based on the percent of acetaminophen undissolved at the 5-, 10-, and 15-min sampling times, it appears that acetaminophen dissolved most rapidly when formulated with the polyethylene glycol 1000 base, followed by polyethylene glycol 4000 and polyethylene glycol 6000 bases, respectively. A t-test was

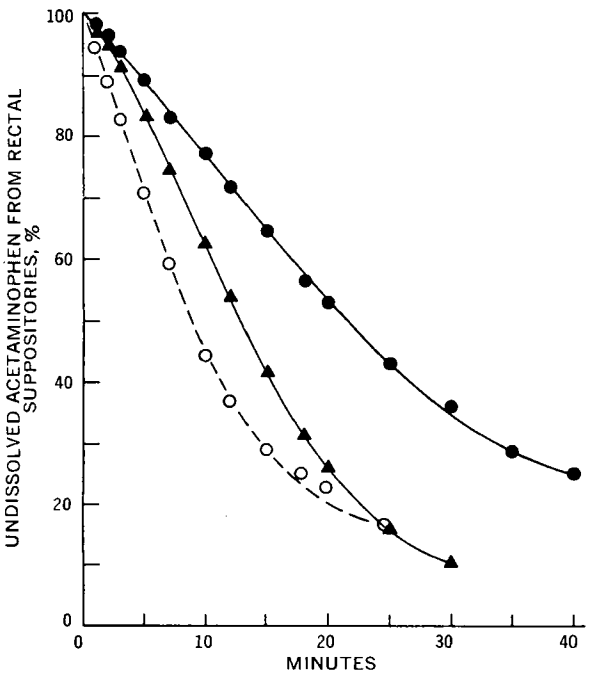

Figure 2—*Dissolution of acetaminophen from three different suppository formulations in 80 ml distilled water at 37° and 25 rpm. Key: ●, polyethylene glycol 6000; ▲, polyethylene glycol 4000; and ○, polyethylene glycol 1000.*

Table III—Results of Statistical Analysis of Dissolution Rates of Each Possible Combination of Pairs of Polyethylene Glycol 1000, 4000, and 6000–Acetaminophen Rectal Suppositories at 5-, 10-, and 15-min Sampling Times

Combination of Polyethylene Glycols	t Value	p
4000 and 1000 (5 min)	11.803	<0.01
6000 and 4000 (5 min)	8.463	<0.05
6000 and 1000 (5 min)	25.935	<0.01
4000 and 1000 (10 min)	6.895	<0.05
6000 and 4000 (10 min)	7.873	<0.05
6000 and 1000 (10 min)	21.280	<0.01
4000 and 1000 (15 min)	5.610	<0.05
6000 and 4000 (15 min)	8.847	<0.05
6000 and 1000 (15 min)	24.086	<0.01

performed on each possible combination of pairs of formulations at three sampling times to determine if there were significant differences in the dissolution profiles of these formulations. The results (Table III) reveal that the differences in the percent undissolved among any two formulations are statistically significant at each interval. These differences were also apparent when the time for half the drug to dissolve (t_{50}) was determined graphically for each formulation. These values were as follows: polyethylene glycol 1000, 8 min; polyethylene glycol 4000, 13 min; and polyethylene glycol 6000, 22 min.

Table IV lists the dielectric constants of the vehicles employed and the total amounts of acetaminophen excreted in 24 hr from each studied formulation. It would appear that, as the dielectric values increase, there is a decline in bioavailability up to some point around a dielectric value of 13 or more, beyond which an increase in bioavailability occurs as observed when water was employed as the vehicle. This effect is more clearly illustrated in Fig. 3, which shows a plot of acetaminophen bioavailability as a function of dielectric constant along with a plot of acetaminophen solubility in water–dioxane mixtures as a function of dielectric constants as reported previously (12). Although it may be rather presumptuous to connect the closed circles with any type of curve, the solid line has been shown to illustrate more clearly the trend and not to assume any type of mathematical relationship. As mentioned previously, it appears that there might be an inflection point in the bioavailability–dielectric relationship in a dielectric range of 10–20 similar to the one that is apparent from the solubility–dielectric curve.

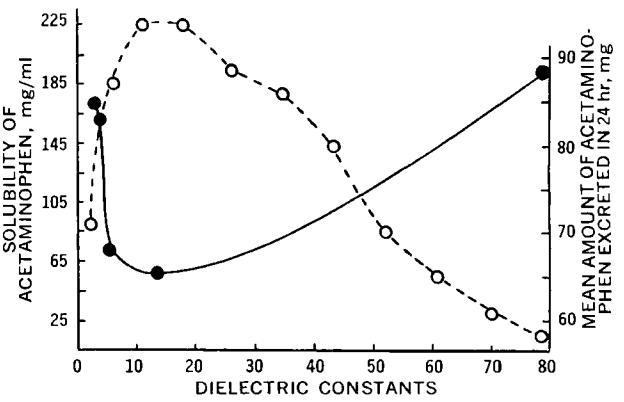

Figure 3—*Comparison of acetaminophen bioavailability and solubility (solubility–dielectric profile from Ref. 12) as a function of vehicle dielectric constant. Key: ○, solubility data; and ●, bioavailability data.*

Table IV—Mean Total Amounts (Milligrams ± Standard Error) of Acetaminophen Excreted in 24 hr for Each Formulation and Dielectric Constants of the Vehicle for Each Formulation

Formulation	Total Amount Excreted, mg	Dielectric Constant
Polyethylene glycol 6000	84.7 ± 1.66	3.0
Polyethylene glycol 4000	83.2 ± 3.03	3.6
Polyethylene glycol 1000	68.0 ± 4.62	5.3
Polyethylene glycol 400	65.7 ± 5.41	13.6
Water	88.2 ± 4.28	78.5

DISCUSSION

The statistical analyses of the results of this study reveal that alteration in the composition of the vehicles employed leads to differences in the absorption pattern of rectally administered formulations of acetaminophen. This conclusion is based on the urinary excretion rates and cumulative urinary excretion of acetaminophen over 24 hr. The rate of urinary excretion is a function of the blood level of the drug and of its metabolites at any given time and, thus, serves as an indication of absorption.

The peak excretion time may be used as an approximate indicator of the relative absorption rates of a drug for comparing different formulations administered by the same route and in equal doses (13). The peak excretion time of 3 hr obtained with the aqueous solution is in accord with significantly higher excretion rates observed during the first 3 hr as compared with the polyethylene glycol bases which showed 4- and 5-hr peak excretion times.

The dissolution rate studies show that one factor controlling the initial rate of absorption is the speed with which the polyethylene glycol bases release the drug into the rectal fluid. Figure 2 shows that the rate of dissolution of polyethylene glycol 1000 suppositories, as reflected by a t_{50} of about 8 min, is faster than polyethylene glycol 4000 (t_{50} = 13 min) and polyethylene glycol 6000 (t_{50} = 22 min). Polyethylene glycol 1000 showed a peak excretion rate at 4 hr, while polyethylene glycol 4000 and 6000 showed peak excretion rates at 5 hr. Although no dissolution was involved with the polyethylene glycol 400 formulation, relatively slower attainment of peak excretion rates as compared to water might be due to slower releasing characteristics of the polyethylene glycol vehicles. Thus, the respective peak excretion times appear to show some correlation with the rates of dissolution, indicating that dissolution may play at least a partial role in the release of acetaminophen from polyethylene glycol suppository bases.

The results of the present study, as illustrated by the cumulative excretion data, appear to indicate that the extent of rectal absorption of acetaminophen is related to its solubility-dielectric profile. This is not an unexpected finding, especially when considered in the light of the previously discussed literature reports (6, 7). Kakemi *et al.* (6) employed solvents with dielectric constants ranging from 10.8 to 53.5. If the assumed bioavailability-dielectric relationship of the present study, as shown in Fig. 3, is correct, then the findings of the two studies would be in agreement in the dielectric range reported previously (6). This would be expected because of the reported similarity in dielectric-related solubility of acetaminophen to the sulfonamides.

Thus, the present findings are in agreement with earlier reports which relate rectal drug absorption to the dielectric properties of the vehicle. However, this study presents a more definitive relationship between rectal absorption and vehicle dielectric properties. All vehicles employed were aqueous or water miscible, thus eliminating the use of a lipoidal substance in the lower dielectric range. Also, the dielectric constants of all vehicles employed were accurately determined, permitting the construction of a plot (Fig. 3) relating bioavailability to the dielectric properties of the vehicle. This relationship below a dielectric constant of 13.6 is rather well defined. It is apparent from Fig. 3 that the decline in the dielectric-related solubility of acetaminophen with decreasing dielectric constants coincides with an increase in the total amount of drug excreted, as might be expected from the previously discussed concepts. Above a dielectric constant of 13.6, the relationship is not as well defined. However, based on the work of Shangraw and Walkling (7) and the results of the present study in the lower dielectric range, a gradual increase in total acetaminophen excretion coinciding with the gradual decline in dielectric-related solubility might be expected in the higher dielectric range.

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