Effect of Vehicle Dielectric Properties on Rectal Absorption of Acetaminophen

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Abstract □ The rectal absorption of acetaminophen from an aqueous suspension, a propylene glycol suspension, and a theobroma oil suppository was measured by urinary excretion. The results are discussed in terms of their relationship to the dielectric constants of the vehicles.

Keyphrases □ Acetaminophen—rectal absorption from aqueous suspension, propylene glycol suspension, theobroma oil suppository, relationship to dielectric constants □ Rectal absorption, acetaminophen—effect of vehicle dielectric constant □ Dielectric constant—role in rectal absorption of acetaminophen in different vehicles

Kakemi *et al.* (1) demonstrated the influence of water-soluble suppository bases on the rectal absorption of sulfonamides in specially prepared rats. Their technique was one of recirculation *in situ* and was designed to elucidate the mechanism of rectal absorption and to evaluate the influence of pharmaceutical materials upon it. These investigators observed that water-miscible compounds such as propylene glycol decreased the absorption of poorly water-soluble sulfonamides through a decrease in lipid–vehicle partition. This decrease in lipid–vehicle partition was related to the dielectric constant of the water-miscible vehicle, because the larger the dielectric constant (or the nearer the dielectric constant to the dielectric constant of water) the smaller the reduction in rectal absorption. In other words, sulfonamides were poorly absorbed from low dielectric media because they were more soluble in that media than in the rectal mucosa.

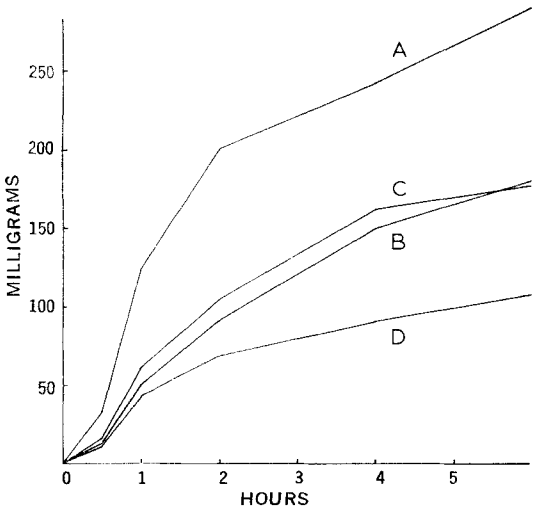

Figure 1—*Urinary excretion means of acetaminophen according to vehicle and route of administration. Key: A, water, oral; B, MCC–CMC gel, rectal; C, theobroma oil, rectal; and D, propylene glycol, rectal.*

Kakemi *et al.* (1) were not able to evaluate the effect of a nonwater-miscible vehicle. Such a vehicle would have a very low dielectric constant—a dielectric constant low enough to be out of the dielectric range required for sulfonamide solubility.

This investigation is an extension of their work; vehicles of all three dielectric ranges—too high, too low, and optimum for solubility—are studied. In addition, this investigation represents an application of their conclusions to a practical formulation–absorption problem in humans.

For human studies, acetaminophen was selected in place of a sulfonamide. Acetaminophen has dielectric-related solubilities similar to those of sulfonamides (2); it is absorbed rectally (3, 4), it can be measured in the urine (3, 5, 6), and it is not known to be sensitizing like the sulfonamides. In addition, detailed pharmacokinetic studies have been reported (5, 6).

Water, with a dielectric constant of 80.37 at 20° (7), had the highest dielectric constant used in this investigation. Propylene glycol represented the optimum range of dielectrics, since it has a dielectric constant of 32.0 at 20° (8). Theobroma oil represented the lower range of dielectrics. The dielectric constant of liquid theobroma oil could be expected to be from 2 to 6, as judged from reported values for vegetable acids and monopalmitin (9).

For comparison, an orally administered solution was included in the study.

EXPERIMENTAL

Materials—Acetaminophen NF micropowder[1] was used in all preparations. Excipients were of USP quality.

Preparation of Dosage Forms—A suspension of acetaminophen, 500 mg./5 ml., buffered to pH 6.0 was prepared in a 4.0% microcrystalline cellulose–carboxymethylcellulose[2] (MCC–CMC) gel by a previously described method (10).

A suspension of acetaminophen in propylene glycol, 500 mg./2 ml., was prepared without additives.

Theobroma oil suppositories of acetaminophen, 500 mg./2 g., were prepared by the fusion process.

The orally administered solution was simply 500 mg. of acetaminophen dissolved in a liter of water.

Urinary Excretion Studies—All subjects were healthy males, ranging from 24 to 39 years of age and from 62 to 95 kg. in weight.

[1] S. B. Penick and Co., New York, N. Y.
[2] Avicel RC, American Viscose Division, FMC Corp., Marcus Hook, Pa.

Table I—Urinary Excretion Means of Acetaminophen ±95% Confidence Limit (mg.)

Vehicle and Route	Number of Subjects	Hours 0.5	1	2	4	6
Water, oral	10	33.3 ±16.7	123 ±36.7	200 ±58.3	242 ±68.3	290 ±75.0
MCC–CMC gel, rectal	10	13.3 ±8.2	44.9 ±28.3	91.5 ±43.3	149 ±58.2	180 ±58.2
Theobroma oil, rectal	10	15.8 ±26.8	60.0 ±41.6	104 ±41.8	162 ±58.2	177 ±29.4
Propylene glycol, rectal	5	11.5 ±8.3	43.3 ±30.0	68.2 ±51.6	90.0 ±63.3	107 ±66.7

The same 10 subjects were used throughout the program. However, only five of these subjects were available for the propylene glycol suspension experiments. These five ranged from 25 to 39 years in age and from 62 to 88 kg. in weight.

The following protocol was utilized. Breakfast was light without coffee or tea. The bowel and bladder were evacuated before inserting the medication. Each subject drank 1 l. of room temperature water after inserting the medication. Urine samples were collected at 0.5, 1, 2, 4, and 6 hr. Abstinence from liquids and drugs during the test was required.

The aqueous and propylene glycol suspensions were administered with the aid of a short piece of polyethylene tubing attached to a glass syringe.

Urine Analysis—Urine analysis for total acetaminophen was by the method of Brodie and Axelrod (11).

Solubility Studies—Ancillary data on the solubility of acetaminophen in the vehicles at 37° were obtained. Each vehicle and an excess of the drug were placed in 75-ml. cylindrical bottles and rotated at 43 r.p.m. for 24 hr. on an apparatus designed for testing sustained-release products. This apparatus is described in the NF (12). For the aqueous and propylene glycol systems, filtered samples were quickly pipeted with warmed pipets, diluted with acidified methanol, and assayed spectrophotometrically at 249 nm. (13).

In the case of theobroma oil, after rotation, the bottle was set in an upright position for 24 hr. in the water bath. The undissolved drug settled to the bottom of the bottle, and a clear zone appeared near the surface of the liquid. After the theobroma oil solidified at room temperature, 500 mg. was scraped from the surface. This material was extracted with warmed acidified methanol. The acidified methanol was then cooled, filtered, and assayed spectrophotometrically at 249 nm.

RESULTS AND DISCUSSION

The urinary recovery means and their 95% confidence limits are listed in Table I. The means themselves are illustrated in Fig. 1.

Table II—*t*-Test Values for Urinary Excretion

X_1, Vehicle and Route	Hours	X_2, Vehicle and Route: Aqueous, Rectal	Theobroma Oil, Rectal	Propylene Glycol, Rectal
Water, oral	0.5	2.0	1.2	1.8
	1	3.1[a]	2.1	2.6[a]
	2	2.9[a]	2.8[a]	2.8[a]
	4	5.3[a]	4.7[a]	5.7[a]
	6	5.6[a]	5.7[a]	7.6[a]
MCC–CMC gel, rectal	0.5		−0.12	0.24
	1		−0.45	0.74
	2		−0.11	0.63
	4		−0.10	3.2[a]
	6		0.17	3.3[a]
Theobroma oil, rectal	0.5			0.18
	1			0.48
	2			0.74
	4			2.8[a]
	6			3.0[a]

[a] Significant difference at 95% level.

The *t*-test values are listed in Table II, and the solubilities are listed in Table III.

As one might expect, in none of the experiments was the total dose excreted within the 6 hr. Even in the case of the oral solution, only 58% of the dose was excreted. With the rectal dosage forms, the percent recovered was much less. Since it was the intent of the investigation to evaluate only the relative bioavailability from the rectal dosage forms and since it was impossible to police both the bowel and bladder habits of the participants for a longer period, a 6-hr. study was considered sufficient.

The excretion rate of acetaminophen from the rectal dosage forms declined during the last sampling period. Since the excretion kinetics of acetaminophen would be the same in all cases, it is difficult to see how the relative bioavailability rankings of the drug from the rectal dosage forms could change at some later time.

From the data, no significant differences in the 0.5-hr. recoveries are observed. After that, the orally administered solution is significantly better than all of the rectal dosage forms. At 4 and 6 hr., the aqueous and theobroma oil vehicles ranked significantly better than the propylene glycol suspension. The differences between the two better formulations and the propylene glycol formulation—whether significant or not—increased with each increasing sampling period. The aqueous and theobroma oil formulations were equivalent at all time periods. By comparing the excretion after 6 hr., the amount excreted from the better formulations was 1.7 times greater than from the propylene glycol formulation.

The solubility of acetaminophen in the various vehicles is in agreement with the predictions of Paruta and Irani (2). At 37°, propylene glycol was 6.6 times and 72 times more effective as a solvent than the aqueous vehicle and theobroma oil, respectively.

The aqueous vehicle contained electrolytes to buffer the system to pH 6.0. These electrolytes would increase the dielectric properties of the system, and their buffer capacity would maintain acetaminophen in its least soluble form (14).

Although rheological evaluations indicated an interaction between acetaminophen and MCC–CMC (10), the solubility studies showed that such an interaction is not particularly significant in regards to *in vitro* availability. The exact role this interaction plays in *in vivo* availability is difficult to assess.

These investigations demonstrated that if acetaminophen is dispersed in a vehicle that has a dielectric constant that meets the dielectric requirement for high solubility, then its rectal absorption is apt to be relatively low. And, if acetaminophen is dispersed in vehicles that have dielectric constants that are too high or too low for high solubility, then its rectal absorption is apt to be relatively high. This work with acetaminophen is a verification and extension of the work of Kakemi *et al.* (1) that was done with sulfonamides in specially prepared rats. This work is also an application of their theories to a practical formulation–absorption problem in humans. However, one must be cautious in making generalizations. Several factors including the alteration of the rectal mucosa, the absorption of the vehicles *per se*, the effects of complexation or binding, and

Table III—Solubility of Acetaminophen in Vehicles at 37°

Vehicle	Solubility
Propylene glycol	156 mg./ml.
MCC–CMC gel	23.6 mg./ml.
pH 6.0 buffer	23.8 mg./ml.
Theobroma oil	2.16 mg./g.

the variation of dosage form mass were not evaluated in this investigation.

SUMMARY

The theories of Kakemi *et al.* (1) that relate the dielectric constants of water-miscible vehicles to rectal absorption have been extended to include a water-immiscible vehicle and have been applied to a practical formulation-absorption problem in humans.

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ACKNOWLEDGMENTS AND ADDRESSES

Received August 17, 1970, from the *School of Pharmacy, University of Maryland, Baltimore, MD 21201*

Accepted for publication October 7, 1970.

The authors acknowledge the financial assistance of the American Viscose Division, FMC Corp., Marcus Hook, Pa.; Eli Lilly and Co., Indianapolis, Ind.; and the Yager Drug Company, Baltimore, Md.

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Extrinsic Cotton Effects of Bishydroxycoumarin when Bound to Bovine Serum Albumin

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Abstract □ The binding of bishydroxycoumarin to bovine serum albumin at pH 7.4 was investigated by circular dichroism and differential absorption. No major conformational changes were observed on binding, but optical activity was induced at wavelengths above 290 nm. and investigated for various drug-to-protein ratios. Several possible explanations for the experimental observations are made.

Keyphrases □ Bishydroxycoumarin—extrinsic Cotton effects when bound to bovine serum albumin □ Albumin, bovine serum—bound bishydroxycoumarin, extrinsic Cotton effects □ Circular dichroism—analysis □ Differential absorption—analysis

Bishydroxycoumarin[1] was found to be over 99% bound to human plasma proteins, even when the concentration in whole blood was 1000 mg./l. (1). Paper electrophoresis studies suggest that the drug is entirely bound to the albumin fraction (2). In this report the binding of bishydroxycoumarin to bovine serum albumin in 0.1 *M* pH 7.4 phosphate buffers is investigated. Other highly protein bound drugs which have shown extrinsic Cotton effects include the *N*-arylanthranilates (3) and the pyrazolone analgesics (4, 5).

MATERIAL AND METHODS

Bishydroxycoumarin USP was used as supplied[2]. The bovine serum albumin was crystallized and lyophilized[3]. All buffer materials were reagent grade. The circular dichroism (CD) spectra were obtained at 25° in 5-, 10-, or 20-mm. cells, using the 6002 attachment to a Cary 60 spectropolarimeter[4]. The dynode voltage was never allowed to exceed 0.35, and the signal-to-noise

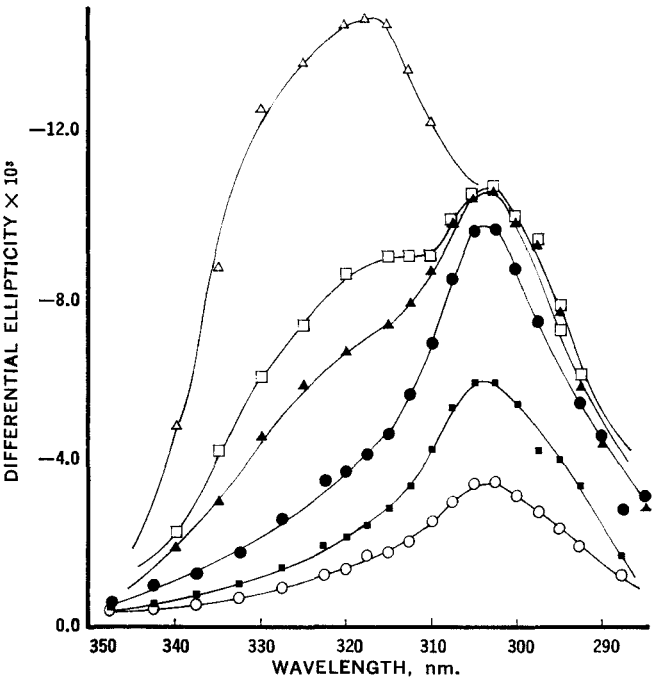

Figure 1—*Extrinsic CD curves for bishydroxycoumarin binding to bovine serum albumin measured in 0.1* M *phosphate buffer, pH 7.4, corrected to 1-cm. pathlength. D/P molar ratios are:* △, *10.26;* □, *6.16;* ▲, *5.13;* ●, *1.44;* ■, *0.82; and* ○, *0.4.*

[1] Dicumarol.
[2] Abbott Laboratories, North Chicago, Ill.
[3] Sigma Chemical Co., St. Louis, Mo.
[4] Cary Instruments, Monrovia, Calif.