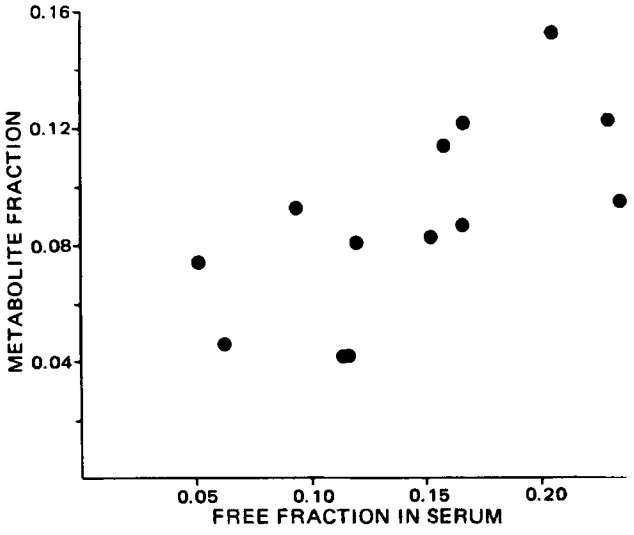

Figure 1—*Relationship between the fraction of a 20-mg/kg iv dose of sulfisoxazole excreted in the urine as metabolites and the free fraction of sulfisoxazole in serum. Data were obtained from 13 rats (6). The correlation coefficient is 0.68;* $p < 0.02$.

types of processes:

$$Cl_T = fk_g(1 - F) + k_s^*(1 - F) + fCl_{m\ \text{intrinsic}} \qquad \text{(Eq. 4)}$$

and the fraction of a dose metabolized is equal to $fCl_{m\ \text{intrinsic}}$ divided by all of the terms on the right side of Eq. 4. Dividing the numerator and denominator of that ratio by f yields:

$$F_m = \frac{Cl_{m\ \text{intrinsic}}}{k_g(1 - F) + Cl_{m\ \text{intrinsic}} + \frac{k_s^*(1 - F)}{f}} \qquad \text{(Eq. 5)}$$

Examination of Eq. 5 reveals that as f increases, F_m also increases. Thus, the fraction of a dose of drug converted to metabolite(s) increases if the serum protein binding of that drug is decreased in blood flowing through the eliminating organs (5)[1]. This conclusion applies only to drugs that are excreted in part by a process whose rate is proportional to the total rather than the free drug concentration in plasma or serum while the rates of other, parallel elimination processes are proportional to the free drug concentration. Sulfisoxazole appears to exhibit such characteristics in rats (6).

In 13 male Sprague–Dawley rats receiving a single intravenous injection of 20 mg of sulfisoxazole/kg, the fraction of the dose recovered in the urine as metabolites ranged from 0.042 to 0.152 and f ranged from 0.0518 to 0.235 (6). Drug concentrations in serum declined biexponentially with no downward curvature, which would occur if renal excretion, the major pathway of elimination, were saturable in the concentration range studied. Reexamination of the experimental data revealed a significant positive correlation between F_m and f (Fig. 1), as predicted by Eq. 5.

One important implication of these findings relates to the mechanism of certain drug interactions. Increased conversion of a drug (A) to its metabolite(s) caused by prior or concomitant administration of another drug (B) usually will be interpreted as resulting from either induction of biotransformation or inhibition of the renal clearance of A. However, if Drug B displaces Drug A from plasma protein binding sites, then the increased biotransformation of Drug A also could occur by the mechanism described in this communication. Another implication concerns the effect of the dose or dosing rate on the metabolic fate of a drug. For drugs that exhibit significant concentration dependence of plasma protein binding (f increases with increasing drug concentration), F_m may increase with increasing dose or dosing rate due to decreased protein binding.

(1) G. Levy and A. Yacobi, *J. Pharm. Sci.*, **63**, 805 (1974).
(2) G. Levy, in "The Effect of Disease States on Drug Pharmacokinetics," L. Z. Benet, Ed., American Pharmaceutical Association, Washington, D.C., 1976, chap. 9.
(3) G. Levy, *J. Pharm. Sci.*, **69**, 482 (1980).
(4) I. M. Weiner, in "Handbook of Physiology, Renal Physiology Section," J. Orloff and R. W. Berliner, Eds., American Physiological Society, Washington, D.C., 1973, pp. 521–554.
(5) U. W. Wiegand and G. Levy, *J. Pharm. Sci.*, **69**, 480 (1980).
(6) A. Yacobi and G. Levy, *ibid.*, **68**, 742 (1979).

Gerhard Levy
Department of Pharmaceutics
School of Pharmacy
State University of New York at Buffalo
Amherst, NY 14260

Received January 14, 1980.
Accepted for publication March 21, 1980.
Supported in part by Grant GM 20852 from the National Institute of General Medical Sciences, National Institutes of Health.

[1] The opposite would occur if biotransformation is blood flow rate limited while the renal excretion rate is proportional to the free drug concentration in plasma.

Polyethylene Glycols as Solvents in Implantable Osmotic Pumps

Keyphrases □ Polyethylene glycols—use as solvents in implantable osmotic pumps □ Solvents—polyethylene glycols, use in implantable osmotic pumps □ Drug delivery systems—implantable osmotic pumps, use of polyethylene glycols as solvents

To the Editor:

Implantable osmotic pumps[1] are useful for short-term delivery of water-soluble drugs and hormones (1–4). However, many compounds such as steroids are too insoluble in water to be administered as aqueous solutions (5). Although 5% ethanol and 5% dimethyl sulfoxide increase the concentration range over which lipophilic molecules can be delivered (6), the maximum dose still is quite low. Polyethylene glycols 400 and 600 are excellent solvents for many steroids (Table I) (1,5) and also are useful *in vivo* since they have very low toxicities (7). The objective of these experiments was to evaluate the suitability of polyethylene glycols as solvents with implantable pumps *in vivo*. Since the polyethylene glycols are known to influence fluid balance *in vivo*, the potential effects of the solvents and the pumps also were examined.

The ability of the pumps to function *in vivo* with polyethylene glycols as solvents was evaluated in two ways. Mineralocorticoids are known to induce the amiloride-

[1] Model 1701, Alza Corp., Palo Alto, CA 94304.

Table I—Solubility of Selected Steroids in Polyethylene Glycols and Soybean Oil [a]

Compound	Solubility at 37°, g/liter: Polyethylene Glycol 400	Polyethylene Glycol 600	Soybean Oil
Aldosterone	83 ± 4 (2)	ND[b]	ND
Corticosterone	26 ± 2 (3)	26 ± 2 (3)	3.0
Desoxycorticosterone acetate	24 ± 2 (3)	28 ± 2 (3)	14
Dexamethasone acetate	45 ± 2 (4)	42 ± 2 (3)	1.4
17β-Estradiol	116 ± 4 (3)	97 ± 4 (3)	1.6
Hydrocortisone	15 ± 2 (3)	24 ± 2 (3)	0.9
Progesterone	27 ± 2 (3)	32 ± 2 (4)	19
Spironolactone	46 ± 3 (4)	44 ± 2 (3)	8
Testosterone	39 ± 2 (4)	42 ± 2 (3)	10

[a] The steroids and the polyethylene glycol solvents were obtained from Sigma Chemical Co., St. Louis, MO 63178. The steroids were suspended in the solvent, warmed to ~80°, and sonicated for dissolution. After storage in sealed vials at 37° for >72 hr, samples were centrifuged at 12,000×*g* for 20 min to pellet any insoluble drug. If insoluble drug was detected, additional solvent was added and the process of warming the solution, sonication, and prolonged storage was repeated until solubility was obtained. Since most values were determined only by approaching apparent equilibrium from a supersaturated solution rather than from both sides, the solubilities cannot be considered as rigorously established equilibrium values. Data with soybean oil (Wesson Oil, Hunt Wesson Foods Inc., Fullerton, CA 92634) are shown for comparison only. Results are given as the mean ± *SEM*; the number in parentheses is the number of independent determinations. [b] ND = not determined.

Table II—Ability of Polyethylene Glycol-Solubilized Steroids to Induce Amiloride-Sensitive Sodium Transport in the Rat Colon [a]

Animals	Treatment	Average Dose, μg/kg/hr	Amiloride-Sensitive Sodium Transport, % total
Control	Untreated	—	9.0 ± 2.8 (8)
Control	Glass rod	—	7.2 ± 1.3 (3)
Control	Pumps with solvent	—	22.6 ± 5.8 (5)
Control	Aldosterone	5.7	76.6 ± 6.4 (4)
Control	Aldosterone + spironolactone	6.0 + 193	36.3 ± 15.8 (3)
Control	Spironolactone	164	15.3 ± 6.6 (3)
ADX	Untreated	—	1.9 ± 1.9 (5)
ADX	Glass rod	—	2.6 ± 0.8 (5)
ADX	Pumps with solvent	—	3.6 ± 0.7 (4)
ADX	Aldosterone	4.3	74.1 ± 15.4 (3)

[a] Male Sprague–Dawley rats with intact adrenal glands (controls) and male bilaterally adrenalectomized rats were maintained on Purina Formulab Chow 5008 (Ralston Purina Co., Richmond, IN 47374) *ad libitum*. The control rats were given 150 m*M* NaCl and 29 m*M* sucrose to drink *ad libitum*. The adrenalectomized animals were given the same solution with 5 m*M* KCl. Drugs were dissolved in polyethylene glycol (Table I) and loaded into osmotic pumps (6). The pumps were placed in the peritoneal cavity of ~150-g rats under ether anesthesia. Glass rods used as sham pumps were 5 × 24-mm pieces of fire-polished soft glass. The descending colon was removed under pentobarbital anesthesia (~75 mg/kg ip) and mounted in a 0.28-cm² Schultz chamber perfused with Krebs–Henseleit balanced salt solution containing 5 m*M* D-glucose (Sigma Chemical Co., St. Louis, MO 63178). The short-circuit current was measured with a conventional circuit using calomel electrodes (catalog No. 13-639-79, Fisher Scientific Co., Pittsburgh, PA 15219) (10) and was displayed on a strip-chart recorder (Brush model 110, Instrument Division, Gould Inc., Cleveland, OH 44114). The amiloride sensitivity of the short-circuit current was the portion of the short-circuit current that was sensitive to 25 μ*M* amiloride added to the mucosal surface of the tissue. Results are shown as the mean ± *SEM*; the number in parentheses is the number of animals.

sensitive sodium transport system in the luminal membrane of the rat colon (8–10). The ability of aldosterone administered by the osmotic pumps to induce the amiloride-sensitive sodium transport system was examined initially. Sodium transport was estimated *in vitro* as the short-circuit current, and amiloride sensitivity was judged by the ability of 25 μ*M* amiloride[2] to inhibit the observed short-circuit current when added to the mucosal side of the tissue (10).

After 3–7 days of aldosterone[3] infusion (Table II), 77% of the short-circuit current was inhibited by amiloride while only 7% of the short-circuit current was sensitive to amiloride in the untreated animals. This effect was due to aldosterone since it could be suppressed by the aldosterone antagonist spironolactone. Since the half-time of the amiloride-sensitive sodium transport system in the absence of aldosterone is ~12 hr (10), aldosterone must have been released from the pumps for the entire infusion period (up to 7 days).

The effectiveness of the pumps also was tested by measuring the weight change of male rats during the administration of 17β-estradiol[3]. Estrogens are known to cause a weight reduction in male rats (11–13). Adrenalectomized (ADX) rats[4] treated for 6 days with pumps containing only polyethylene glycol gained 32.2 ± 6.6 g (mean ± *SEM*, $n = 3$); the adrenalectomized rats treated with 145 μg of 17β-estradiol/kg/hr lost 22.3 ± 5.8 g ($n = 3$).

These results indicate that polyethylene glycols are effective solvents for use with osmotic pumps *in vivo*.

Although relatively large volumes of polyethylene glycol (~3 ml/kg) may perturb the fluid balance when injected into the peritoneal cavity (14, 15), the quantity of polyethylene glycol delivered by the pumps (5–10 μl/kg/hr) (1) probably is too low for this problem to be significant. The slight elevation of amiloride-sensitive sodium transport observed with control animals[4] with intact adrenal glands when compared to control animals with sham pumps (glass rods) (Table II) is due to effects of the pumps. The pumps probably act as fluid sinks, reducing the extracellular volume, stimulating the renin–angiotensin system, and causing a slight elevation of the endogenous aldosterone levels. This increase in the circulating aldosterone concentration causes the amiloride sensitivity of the colon to be elevated over that of the sham pump-treated controls (23 *versus* 7%). The renin–angiotensin–aldosterone system probably is responsible for this effect since it was reduced by treatment with spironolactone (Table II) and was abolished in the adrenalectomized animals. Although the pump-mediated increase in the activity of the renin–angiotensin–aldosterone system is small, these results serve to advise potential users of osmotic pumps that sufficient controls are important.

Osmotic pumps are useful for studies of drug efficacy *in vivo* where the actual rate of drug treatment must be maintained over a relatively long period to compare the potency of different compounds adequately. When utilized with appropriate controls, polyethylene glycols greatly expand the usefulness of these pumps to otherwise insoluble lipophilic compounds.

[2] Obtained as amiloride hydrochloride as a gift from Merck Sharp & Dohme Research Laboratories, Rahway, NJ 07065.
[3] Sigma Chemical Co., St. Louis, MO 63178.
[4] Zivic Miller Laboratories, Allison Park, PA 15101.

(1) F. E. Yates, Ed., *Special Delivery*, **3**(1), 2 (1979).
(2) E. Wei and H. Loh, *Science*, **193**, 1262 (1976).
(3) C. Y. Bowers and K. Folkers, *Biochem. Biophys. Res. Commun.*, **72**, 1003 (1976).
(4) H. M. Pinedo, D. S. Zaharko, J. Bull, and B. A. Chadner, *Cancer Res.*, **37**, 445 (1977).
(5) B. W. Barry and D. I. D. El Eini, *J. Pharm. Pharmacol.*, **28**, 210 (1976).
(6) Alzet Osmotic Minipump Instruction Manual, Alza Corp., Palo Alto, Calif., 1976.
(7) W. Bartsch, G. Sponer, K. Dietmann, and G. Fuchs, *Arzneim.-Forsch.*, **26**, 1581 (1976).
(8) P. C. Will and U. Hopfer, *Fed. Proc. Fed. Am. Soc. Exp. Biol.*, **38**, 1240 (1979).

(9) U. Hopfer and P. C. Will, *ibid.*, **38**, 1060 (1979).
(10) P. C. Will, J. L. Lebowitz, and U. Hopfer, *Am. J. Physiol.*, in press.
(11) J. Menard, A. Malmejac, and P. Milliez, *Endocrinology*, **86**, 774 (1970).
(12) O. M. Helmer and R. S. Griffith, *ibid.*, **51**, 421 (1952).
(13) H. Burrows, "Biological Actions of Sex Hormones," 2nd ed., Cambridge University Press, Cambridge, England, 1949, pp. 160, 354, 443–445.
(14) A. E. Abdelaal, P. F. Mercer, and G. J. Mogenson, *Can. J. Physiol. Pharmacol.*, **52**, 362 (1974).
(15) J. T. Fitzsimons, *J. Physiol.*, **159**, 297 (1961).

Peter C. Will
Ronald N. Cortright
Ulrich Hopfer ˣ
Department of Anatomy and Developmental Biology Center
Case Western Reserve University
Cleveland, OH 44106

Received October 29, 1979.
Accepted for publication March 24, 1980.
Supported by Grant AM-08305 from the U.S. Public Health Service.

Disintegration Test for Hard Gelatin Capsules

Keyphrases □ Disintegration—hard gelatin capsules, modification of USP and NF tests for tablet disintegration □ Dosage forms—hard gelatin capsules, disintegration test, modification of USP and NF tests for tablet disintegration

To the Editor:

A proposed disintegration test procedure for capsules was published in the USP XX Comment Proof (Vol. 3, No. 56) dated August 14, 1978. This procedure was based on a series of collaborative studies conducted by the Disintegration Test Review Committee of the Pharmaceutical Manufacturers Association (PMA) Quality Control Section. Highlights of these studies are presented in this communication.

The USP and NF describe disintegration tests for five tablet categories. The PMA project was aimed at developing a similar test for hard gelatin capsule products using the apparatus and methodology for tablet disintegration with as few changes as necessary. Three test samples (No. 2 hard gelatin capsules containing 0.5, 1.0, and 1.5% magnesium stearate in lactose) were used in the studies to evaluate procedure variables. Comments on each variable follow.

A cross section of disintegration baskets used in industry was examined. The baskets generally fell into two categories: those with notched shafts and those having shafts equipped with hooks. The former type provides a rigid mounting to the motorized device, and the motion is primarily vertical; the latter basket type provides a nonrigid attachment where the motion is both vertical and rotational. Studies showed that the mounting mode had no influence on the test results. Disintegration times were identical, within normal variation, regardless of the type of mounting used.

The disintegration time of the three test samples could not be differentiated when the plastic disks described in the USP and NF were placed into the basket-rack assembly. The disintegration time for each sample was ~3 min. By eliminating the disks and placing a 10-mesh wire screen on top of the baskets to retain the capsules within the tubes, the disintegration times for the 0.5, 1.0, and 1.5% samples were 12, 25, and 39 min, respectively.

The compendia are not specific about the disintegration test vessel. Committee members reported that both the size of the vessel and the volume of the test vehicle affected the hydrodynamics of the system, thereby influencing the disintegration rate. A 1000-ml, low-form beaker containing ~900 ml of medium was the most convenient and compatible with the dimensions of the basket-rack assembly.

Purified water was a satisfactory test vehicle for the three samples. Reproducibility in disintegration time was improved by the addition of 0.1% benzalkonium chloride. The use of simulated gastric fluid was investigated, but it was reported that hydrogen chloride vapors emanating from the fluid slowly corrode the equipment. Because of variation in the composition of compendial capsule products, collaborators recommended that both the test medium and the disintegration time limit be specified in the individual monographs.

The Committee observed that the longer the path through which the basket travels in its vertical motion, the more rapid is the disintegration time. The USP and NF specify a stroke length of 5–6 cm. In a study involving one test specimen (1.0% magnesium stearate in lactose with an average disintegration time of 25 min), the disintegration time decreased by almost 6 min when the stroke was adjusted from the lower limit, 5 cm, to the upper limit, 6 cm. Therefore, a stroke length of 5.3–5.7 cm was recommended.

The final procedure was submitted to the USP after it was found to be workable in the laboratories of 13 PMA-member companies.

Jerry Polesuk, Chairman
Disintegration Test Review Committee
PMA Quality Control Section

Received August 20, 1979.
Accepted for publication March 14, 1980.
Inquiries may be directed to the author at the Quality Assurance Department, Sandoz Pharmaceuticals, East Hanover, NJ 07936.

Effect of Smoking on Binding of Lidocaine to Human Serum Proteins

Keyphrases □ Lidocaine—effect of smoking on binding to human serum proteins □ Protein binding—lidocaine, effect of smoking, human serum □ Smoking—effect on binding of lidocaine to human serum proteins

To the Editor:

Cigarette smoking can have striking effects on the disposition of theophylline (1, 2), propranolol (3), and other drugs (4, 5). These changes generally have been ascribed to increased intrinsic hepatic clearance secondary to enzyme induction. However, other mechanisms may be operative. This communication describes the apparent effect

0022-3549/80/0600-0749$01.00/0