Dissolution and Absorption of the Antineoplastic Agent Ellipticine

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Abstract □ Ellipticine, a poorly water-soluble alkaloid, is active in several experimental tumor systems. Marked solubility increases were produced by polyvinylpyrrolidone of varying molecular weights (10,000–160,000) and were optimal (~13 mg/ml at 25°) with polyvinylpyrrolidone mol. wt. 10,000. Dissolution of ellipticine–polyvinylpyrrolidone (1:22 w/w) tablets in simulated gastric juice was superior to that of ellipticine hydrochloride. Release rates were controlled by combinations of polyvinylpyrrolidone polymers without affecting maximum dissolution at 37°. Physiological disposition of ellipticine–polyvinylpyrrolidone was compared with that of the hydrochloride salt and ellipticine in suspension following oral administration at 250 mg/kg in fasted mice. In comparison to the suspension, ellipticine tissue levels were about threefold higher with polyvinylpyrrolidone or hydrochloride preparations. Antitumor activity of the three preparations was evaluated intraperitoneally and orally *versus* L-1210 leukemia. The optimal dose of ellipticine–polyvinylpyrrolidone and ellipticine hydrochloride was lower than that of the suspension and suggested improved absorption.

Keyphrases □ Ellipticine—dissolution and GI absorption, effect of polyvinylpyrrolidone □ Dissolution—ellipticine, effect of polyvinylpyrrolidone □ Absorption, GI—ellipticine, effect of polyvinylpyrrolidone □ Polyvinylpyrrolidone—effect on dissolution and GI absorption of ellipticine □ Antineoplastic agents—ellipticine, dissolution and GI absorption, effect of polyvinylpyrrolidone

The plant alkaloid ellipticine (1) possesses marked antitumor activity *versus* transplantable murine tumors following intraperitoneal or oral administration. However, intravenous administration of ellipticine as the hydrochloride salt resulted in hemolysis, hypotension, and arrhythmias (2). Addition of citrate markedly reduced hemolysis but did not influence the cardiovascular side effects (3).

Since the intensity of the toxic effects was related to the administration rate, studies were directed toward an oral formulation. Ellipticine has a water solubility of about 1 mg/liter, which was markedly enhanced by polyvinylpyrrolidone. Solubility was affected by the molecular weight of the polymer and was optimal (about a 10^5-fold increase) at mol. wt. 10,000. This report concerns the development of an oral formulation and the influence of the preparation on physiological disposition and antitumor activity of ellipticine.

EXPERIMENTAL

Ellipticine[1] (NSC-71795) and polyvinylpyrrolidone mol. wt. 10,000[2], 40,000[2], and 160,000[3] were used. Other compounds were USP grade and were used without further purification.

Physiological Disposition—Male BDF-1 mice, 18–24 g, were fasted for 16 hr before and up to 12 hr after drug administration *via* oral intubation at 250 mg of ellipticine base/kg. Ellipticine, 12.5 mg/ml, was administered at 2% body weight in four formulations: a solution in 30% polyvinylpyrrolidone mol. wt. 10,000, a solution of the hydrochloride salt, a suspension in polyvinylpyrrolidone mol. wt. 10,000–160,000 (4:1), and a suspension in a 0.5% carboxymethylcellulose sodium vehicle.

Mice were killed by cervical dislocation in sets of two each at 2, 4, 8, 12, or 24 hr after oral administration. The liver, kidneys, heart, and spleen were rapidly excised, rinsed with 0.9% sodium chloride, and immediately frozen or homogenized. Frozen samples were stored at −20° and processed within 1 week. Blood was collected in a citrated syringe from a jugular vein.

The method of Hardesty *et al.* (4) was used with modification for tissue extraction and estimation of ellipticine equivalents. Liver and kidney samples were homogenized with four volumes of 0.05 *M* pH 7.4 phosphate buffer and extracted with two volumes of water-saturated ethyl acetate. After centrifugation at 6000 rpm for 20 min, the ethyl acetate layer was mixed with an equal volume of 0.01 *N* HCl. The acid layer was separated by centrifugation at 6000 rpm for 20 min, and the absorbance of this solution was determined[4] at 303 nm *versus* 0.01 *N* HCl. Estimation of ellipticine in 0.01 *N* HCl altered the λ_{max} of peak absorbance from 283 nm in ethyl acetate to 303 nm and improved sensitivity of the assay since the background absorbance at 303 nm was much less than at 283 nm. Spleen and heart samples were homogenized in about 10 volumes of 0.05 *M* phosphate buffer at pH 7.4.

Tissues from untreated mice were extracted as described and served as controls for hydrochloride- and suspension-treated animals. For the polyvinylpyrrolidone group, mice were injected with equivalent volumes of polyvinylpyrrolidone mol. wt. 10,000 and sacrificed 8 hr later; the tissues were extracted as described. Polyvinylpyrrolidone did not influence the background absorbance at 303 nm.

Before the disposition studies, recovery experiments were conducted. Ellipticine was added to ice-cold homogenates of all tissues to yield a 0.5-μg/ml mixture, and the tissues were extracted as described. Recovery ranged from 92 to 98%. Corrections for recovery were not applied, and each value represents the mean of three determinations. Total ellipticine equivalents were obtained after correction for background from a Beer-type plot ($E^{303}_{0.01\ N\ HCl}$ = 52,000) and expressed as micrograms of ellipticine equivalents per gram of tissue (wet weight).

Antitumor Evaluation—The effects of formulation variables on the antitumor activity of ellipticine were evaluated in the transplantable L-1210 tumor system according to National Cancer Institute protocols (5). Ellipticine was prepared as a suspension in 0.9% sodium chloride and in polyvinylpyrrolidone mol. wt. 10,000–160,000 (4:1) or as a solution of the hydrochloride salt and administered at 2% body weight daily for 9 days commencing 24 hr after intraperitoneal implant of 10^5 tumor cells. Each preparation was administered by intraperitoneal and oral routes. The data are expressed as the percent increase in lifespan (ILS) of drug-treated over vehicle-treated mice.

Formulation Studies—All tablet formulations were prepared to provide 25 mg of ellipticine base, 50 mg of microcrystalline cellulose, 1.2 mg of calcium stearate, and a total weight of 600 mg. Adjustments to formulas were made with polyvinylpyrrolidone or mannitol. All components were triturated thoroughly in a mortar. Tablets were prepared by direct compression on a single-punch tablet machine[5] equipped with a 1.43-cm die, and they exhibited a uniform yellow appearance. The ellipticine content was within 5% of the labeled amount.

The dissolution of ellipticine from these tablet mixtures was determined using essentially the rotating-basket method (6). A flask containing 500 ml of dissolution medium was immersed in a constant-temperature water bath at 37 ± 0.5°. After the tablet was inserted, the basket was rotated horizontally at 100 rpm. The geometry of the system was maintained by appropriate markings. At specified intervals, 5.0 ml was removed and filtered through a 0.22-μm membrane. The filtrate was analyzed spectrophotometrically at 293 nm after dilution with 0.05 *M* pH 7.4 phosphate buffer. The volume of the dissolution bath was maintained by replacement with an equal volume of medium.

[1] Drug Research and Development Program, National Cancer Institute.
[2] Aldrich Chemical Co., Milwaukee, Wis.
[3] GAF Corp., New York, N.Y.
[4] Cary 15 recording spectrophotometer, Cary Instruments, Monrovia, Calif.
[5] Stokes, Warminster, Pa.

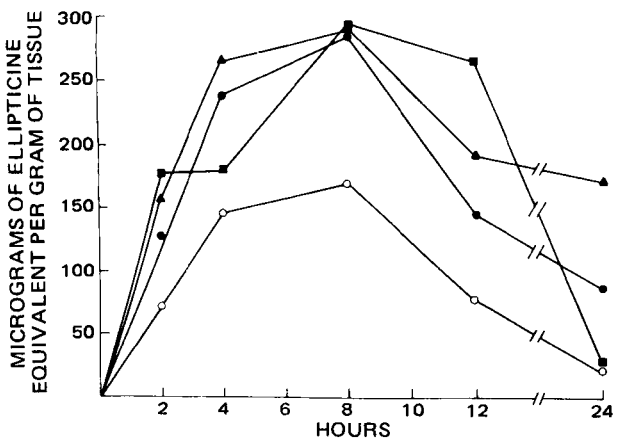

Figure 1—*Effect of formulation on the disposition of ellipticine in the liver. Ellipticine was administered to fasted mice at 250 mg/kg po by gavage in four formulations. Key: ●, ellipticine hydrochloride solution; ▲, ellipticine solution in 30% polyvinylpyrrolidone mol. wt. 10,000; ■, ellipticine suspension in 30% polyvinylpyrrolidone mol. wt. 10,000–160,000 (4:1); and ○, ellipticine suspension in 0.5% carboxymethylcellulose sodium.*

RESULTS

Ellipticine, a poorly water-soluble antineoplastic agent, is believed to exert its antitumor effect *via* intercalation with DNA (7). However, severe hemolysis and cardiovascular effects following intravenous administration have limited its utility. An oral formulation was sought that would provide excellent, but gradual, absorption of ellipticine. Marked improvement (about 10,000-fold) in ellipticine solubility could be achieved by salt formation or by complexation with polyvinylpyrrolidone mol. wt. 10,000 (8). The effect of these approaches on the pharmacological disposition and antitumor activity of oral ellipticine was evaluated in BDF-1 mice, the host for the L-1210 transplantable murine leukemia. The levels of ellipticine equivalents were obtained over 24 hr in the liver, kidneys, blood, spleen, and heart after administration of the drug as a solution or suspension.

Tissue levels in liver are temporally and qualitatively representative of the other tissues and are described in Fig. 1. Peak levels were observed at 8 hr after drug administration regardless of formulation. Ellipticine was rather rapidly absorbed and persisted for at least 12 hr in the liver. The drug levels following administration of the polyvinylpyrrolidone preparations were slightly higher or equivalent to the hydrochloride preparation, but both formulations provided tissue levels two- to threefold higher than the values observed in the suspension-treated mice.

Figure 2 presents the data for the kidneys. Although the tissue levels were lower, the relationship between the various formulations was the same. The drug levels in polyvinylpyrrolidone and hydrochloride groups

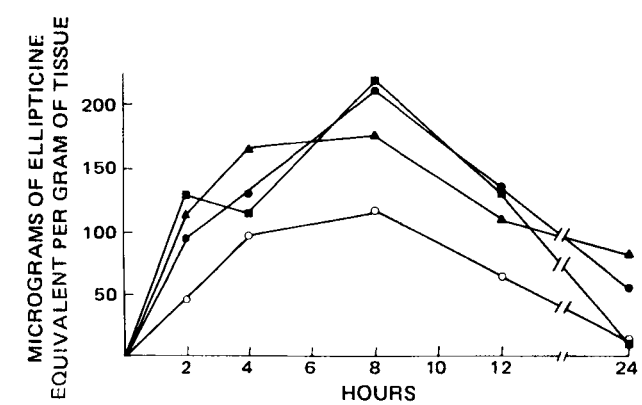

Figure 2—*Effect of formulation on the disposition of ellipticine in the kidneys. Ellipticine was administered to fasted mice at 250 mg/kg po by gavage in four formulations. Key: ●, ellipticine hydrochloride solution; ▲, ellipticine solution in 30% polyvinylpyrrolidone mol. wt. 10,000; ■, ellipticine suspension in 30% polyvinylpyrrolidone mol. wt. 10,000–160,000 (4:1); and ○, ellipticine suspension in 0.5% carboxymethylcellulose sodium.*

Table I—Effect of Formulation on the Physiological Disposition of Ellipticine [a]

Hours	Ellipticine Hydrochloride	Ellipticine–Polyvinylpyrrolidone Solution	Ellipticine–Polyvinylpyrrolidone Suspension	Ellipticine Suspension
		Spleen		
2	81	114	203	45
4	205	225	199	159
8	267	336	276	126
12	392	315	243	178
24	242	292	62	49
		Heart		
2	33	37	44	16
4	34	38	35	27
8	52	65	50	21
12	49	49	28	25
24	24	36	Not detectable	Not detectable
		Blood		
2	7.3	7.5	5.5	4.4
4	9.6	8.0	5.0	4.6
8	10.9	22.3	5.8	4.6
12	4.5	5.0	4.0	3.1
24	11.0	5.0	0.9	Not detectable

[a] Ellipticine was administered at 250 mg/kg po by gavage at 2% body weight to fasted mice. See text for description of formulation. Each value represents the mean of three determinations. Data are expressed as micrograms of ellipticine equivalents per gram of tissue (wet weight).

were very similar and about double the suspension-treated group. The results for spleen, heart, and blood samples are described in Table I. Drug levels in the spleen were intermediate between the liver and kidneys. In addition, the drug levels remained elevated at 12 hr and were the peak values in two instances. A similar observation was reported with daunorubicin, another intercalating agent (9). In contrast to the other tissues, the levels of ellipticine in the heart were low but similar with respect to the time of peak concentration and levels among the different formulations.

Blood ellipticine levels were uniformly low at all time periods and below detectable limits (0.25 μg/ml) at 24 hr in the suspension group. A high tissue to blood ratio was reported by other workers investigating the disposition of intercalating agents (10). The differences in tissue levels over the 4–12-hr period do not appear similarly reflected in blood levels.

The antitumor effects of three preparations *versus* the L-1210 murine leukemia were compared using several routes and administration schedules. The data are presented as the percent increase in median survival of the drug-treated animals over the vehicle-treated control group and are described for the daily 1–9 schedules by intraperitoneal and oral routes in Table II. The optimal doses of ellipticine by the intraperitoneal route for polyvinylpyrrolidone, hydrochloride, and suspension groups were 12.5, 12.5, and 25 mg/kg, respectively. Following oral

Table II—Effect of Ellipticine Formulation on Antitumor Activity [a] (Percent ILS)

Dose, mg/kg/day	Ellipticine Hydrochloride	Ellipticine–Polyvinylpyrrolidone Suspension	Ellipticine Suspension
	Intraperitoneal, Days 1–9		
25	4	27	137
12.5	116	114	95
6.2	57	69	59
3.1	24	40	52
	Oral, Days 1–9		
50	13	31	55
25	69	72	41
12.5	37	38	11
6.2	30	22	19

[a] Male mice were inoculated intraperitoneally with 10^5 L-1210 cells on Day 0. Drug formulations were administered intraperitoneally or orally on Days 1–9. Data are expressed as the percent increase in survival of drug-treated over vehicle-treated mice.

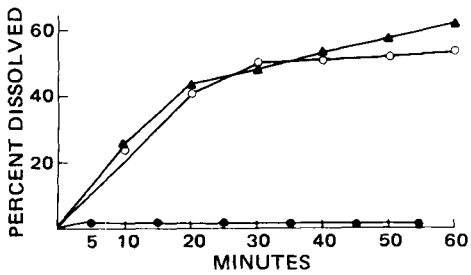

Figure 3—*Dissolution of ellipticine tablets at 37° in water. Key: ●, ellipticine–mannitol; ○, ellipticine–polyvinylpyrrolidone mol. wt. 10,000 (1:15.7); and ▲, ellipticine–polyvinylpyrrolidone mol. wt. 10,000 (1:22).*

administration, the optimal dose was one level higher in all cases. Within a particular route, the maximum ILS was quite similar among the preparations. Since a minimum ILS of 50% is required for activity (5), all preparations meet criteria in this tumor system.

Pharmacological disposition and antitumor studies indicated that polyvinylpyrrolidone and hydrochloride formulations of ellipticine were superior to ellipticine base. Therefore, tablet formulations incorporating these features were prepared and evaluated using *in vitro* dissolution at 37°. In Fig. 3, the dissolution rates of ellipticine tablets with polyvinylpyrrolidone mol. wt. 10,000 in ratios of 1:15.7 and 1:22 were plotted and compared to ellipticine tablets without polyvinylpyrrolidone. The inherent low solubility of ellipticine was evident from the dissolution data. The initial dissolution of the polyvinylpyrrolidone tablets was rapid and essentially the same at the two polyvinylpyrrolidone ratios. After 15 min, the rate slowed considerably, and dissolution of the 1:22 ratio was about 10% higher than the 1:15.7 preparation.

This experiment suggests a critical role of polyvinylpyrrolidone in the mixture. Presumably, polyvinylpyrrolidone initially is in high concentration at the liquid interface but dissolves rapidly. The dissolution rate of ellipticine thus subsides as the polyvinylpyrrolidone diffuses. An attempt was made to improve dissolution by decreasing the diffusion of the polymer *via* inclusion of a higher molecular weight, more viscous polyvinylpyrrolidone. In Fig. 4, the dissolution of ellipticine–polyvinylpyrrolidone mixtures in a 1:22 ratio is presented. Twenty percent of the polyvinylpyrrolidone portion was either mol. wt. 40,000 or 160,000. The dissolution plots for polyvinylpyrrolidone mol. wt. 10,000 alone and mol. wt. 10,000–40,000 (4:1) are essentially superimposable, and the amount dissolved was less than was observed with polyvinylpyrrolidone mol. wt. 10,000–160,000 (4:1). Although the plot is nonlinear with the last-mentioned preparation, the dissolution was more gradual than with polyvinylpyrrolidone mol. wt. 10,000 alone, suggesting that the increased viscosity of polyvinylpyrrolidone mol. wt. 160,000 decreases polymer diffusion from the tablet matrix.

In the diffusion layer model (11), the rate is influenced by the solubility of free drug and drug complex plus the diffusion coefficients of all polymeric species. In this case, the role of the free drug is negligible due to its low intrinsic solubility. The concentration of bound or solubilized drug

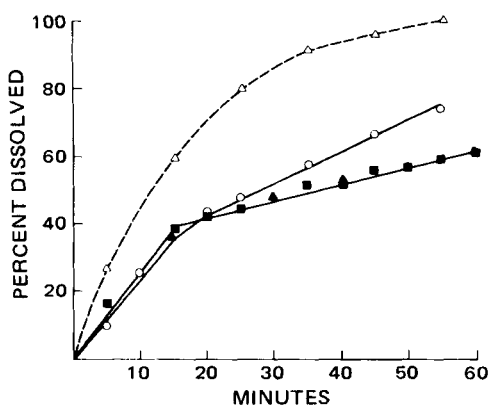

Figure 4—*Dissolution of ellipticine–polyvinylpyrrolidone (1:22) tablets at 37° in water. Key: ▲, polyvinylpyrrolidone mol. wt. 10,000; ■, polyvinylpyrrolidone mol. wt. 10,000–40,000 (4:1); ○, polyvinylpyrrolidone mol. wt. 10,000–160,000 (4:1); and △, polyvinylpyrrolidone mol. wt. 10,000–160,000 (4:1) using simulated gastric juice.*

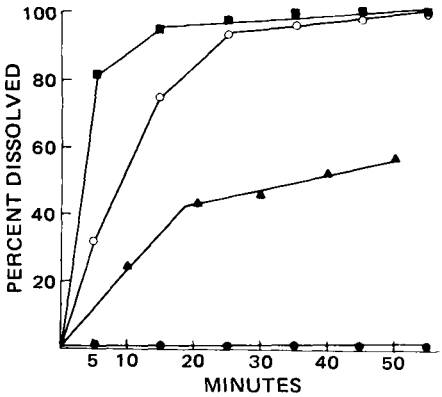

Figure 5—*Effect of media on the dissolution of ellipticine tablets at 37°. Key: ▲, ellipticine–polyvinylpyrrolidone mol. wt. 10,000 (1:22) in water; ○, ellipticine–polyvinylpyrrolidone mol. wt. 10,000 (1:22) in 2% polyvinylpyrrolidone; ●, ellipticine–mannitol in water; and ■, ellipticine–mannitol in 2.1% polyvinylpyrrolidone.*

at the interface depends on the solubility of unbound forms of drug in the diffusion layer and of polymers at the interface. Polyvinylpyrrolidone mol. wt. 160,000 molecules presumably render the diffusion layer more viscous and retard bulk flow of polyvinylpyrrolidone, thus enhancing the formation of drug–polymer complexes of high solubility.

To evaluate these assumptions, dissolution was carried out in polyvinylpyrrolidone 2.1 or 2% medium using tablets containing ellipticine base plus mannitol or ellipticine–polyvinylpyrrolidone mol. wt. 10,000 (1:22) ratio (Fig. 5). The final polyvinylpyrrolidone concentration in the medium was 2.1%. Dissolution data for the same tablets in water are presented for comparison. The ellipticine–mannitol tablet dissolved completely in polyvinylpyrrolidone in about 15 min. In contrast, the polyvinylpyrrolidone (1:22) tablet dissolved more slowly and reached an equivalent level in 25–35 min. With ellipticine–polyvinylpyrrolidone tablets, the presence of polyvinylpyrrolidone in the diffusion layer imparted a barrier to the boundary movement of ellipticine, thus impairing dissolution.

To approximate the *in vivo* environment more closely, dissolution studies were conducted on the ellipticine–polyvinylpyrrolidone mol. wt. 10,000–160,000 tablet and the ellipticine hydrochloride tablet in simulated gastric juice (12) at 37°. Complete dissolution of the polyvinylpyrrolidone preparation was achieved within 1 hr (Fig. 4). The enhanced dissolution was due in part to pH and formation of the protonated form of ellipticine. Surprisingly, the dissolution of ellipticine hydrochloride was markedly depressed (Fig. 6). Although dissolution was essentially complete in 5–10 min, only about 40% of the available ellipticine dissolved.

Since simulated gastric juice contains hydrochloric acid and sodium chloride at a chloride concentration of ~110 mEq/liter, the dissolution of ellipticine hydrochloride tablets was evaluated in 0.1 *N* HCl, 0.1 *N* H_2SO_4, and water. Hydrochloric acid also markedly depressed the dissolution of ellipticine. However, the dissolution of the same tablet in water or 0.1 *N* H_2SO_4 was rapid and plateaued at about 80% (Fig. 6). These data demonstrate that the chloride ion rather than pH depresses ellipticine hydrochloride dissolution; under conditions simulating the gastric en-

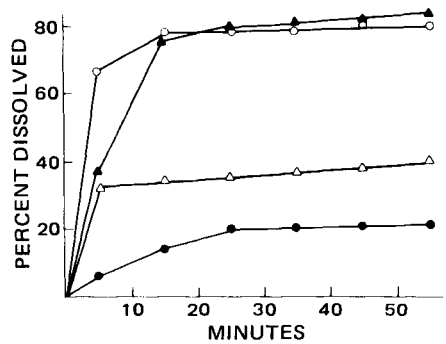

Figure 6—*Effect of media on the dissolution of ellipticine hydrochloride tablets at 37°. Key: ●, 0.1 N HCl; △, simulated gastric juice; ○, water; and ▲, 0.1 N H_2SO_4.*

vironment, dissolution of the ellipticine–polyvinylpyrrolidone preparation is essentially complete.

Similarly, Agharkar *et al.* (13) demonstrated that the dissolution of α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol, an antimalarial agent, was markedly depressed in 0.1 *N* HCl but not in an equivalent concentration of 0.1 *N* H_2SO_4. The solubility of this antimalarial was inversely related to the chloride-ion concentration, and the results were attributed to a common ion effect.

DISCUSSION

Several investigators described increases in solubility of various compounds by polyvinylpyrrolidone (14, 15), but the effect of this interaction on the dissolution rate has been varied. Polyvinylpyrrolidone reduced salicylic acid dissolution, and this effect was attributed to the increased viscosity or formation of a polyvinylpyrrolidone–salicylic acid complex (16). Dissolution rates of ephedrine hydrochloride, potassium chloride, and sodium chloride from compressed disks also were decreased by polyvinylpyrrolidone (17, 18). In contrast, Simonelli *et al.* (19) described enhanced solubility and dissolution of polyvinylpyrrolidone–sulfathiazole mixtures or coprecipitates. Solid dispersions of reserpine, a poorly water-soluble drug, with polyvinylpyrrolidone enhanced its *in vitro* dissolution and absorption. In addition, a polyvinylpyrrolidone–digitoxin coprecipitate exhibited enhanced dissolution and absorption as indicated by a decrease in the LD_{50} value (20, 21).

Polyvinylpyrrolidone also increased dissolution of hydroflumethiazide and hydrochlorothiazide (22, 23). Interestingly, the absorption of the drug in physical mixture with polyvinylpyrrolidone was superior to the coprecipitate or free drug (23). Simonelli (24) previously reported that ellipticine solubility was enhanced by preparation of a polyvinylpyrrolidone coprecipitate and used this technique to prepare a product for intravenous use. Toxicity inherent with intravenous ellipticine necessitated an alternative administration route.

The marked enhancement of ellipticine absorption by polyvinylpyrrolidone was investigated orally and was compared with salt formation. Absorption of ellipticine as a solution in polyvinylpyrrolidone mol. wt. 10,000 or as a mixture with mol. wt. 10,000–160,000 (4:1) was two- to threefold higher than that of the parent drug and equivalent to or slightly better than that of the hydrochloride salt. The polyvinylpyrrolidone mol. wt. 10,000–160,000 (4:1) mixture also exhibited antitumor activity by oral and intraperitoneal routes. When using the optimal dose level in milligrams per kilogram as an index of absorption, the optimal dose was one level less than that of the suspension of free drug and equivalent to that of the hydrochloride salt. The intraperitoneal data for polyvinylpyrrolidone and hydrochloride preparations indicate, however, that oral absorption is incomplete regardless of formulation. The optimal dose was one level lower than the oral one, and the response in terms of an increase in lifespan was higher. Similar comparisons of routes of administration were not carried out in the distribution studies. Mice receiving polyvinylpyrrolidone and hydrochloride preparations of ellipticine at 250 mg/kg ip died within 24 hr.

Since the biological experiments indicated comparability between polyvinylpyrrolidone and hydrochloride preparations, ellipticine dissolution from several tablet formulations was evaluated. As expected because of the marked effect of polyvinylpyrrolidone on the low intrinsic solubility of ellipticine (8), the dissolution was related to the polyvinylpyrrolidone concentration in the tablet. Dissolution data from polyvinylpyrrolidone mixtures were compatible with the diffusion layer model and demonstrated that drug release could be enhanced *in vitro* by inclusion of high and low molecular weight polymeric material.

Extrapolation of biological data described in this report to larger animals may be difficult since dissolution was avoided by administering two preparations in solution (polyvinylpyrrolidone mol. wt. 10,000 and hydrochloride salt). In contrast to the mouse, the dog or monkey would be administered ellipticine in a tablet. Marked differences in dissolution were observed *in vitro* in simulated gastric juice with tablet formulations similar to those evaluated *in vivo*. Studies are in progress to compare the absorption of ellipticine in polyvinylpyrrolidone mol. wt. 10,000–160,000 (4:1) with that of the hydrochloride preparation in dogs or monkeys.

REFERENCES

(1) M. Hayat, G. Mathe, E. Chenu, M. M. Janot, P. Potier, N. Dat-Xuong, A. Gave, T. Sevenet, J. Poisson, J. Miet, J. Le Men, F. Le Goffic, A. Gouyette, A. Ahond, L. K. Dalton, and T. A. Connors, *Biomedicine*, **21**, 101 (1974).

(2) E. Herman, J. Vick, and B. Burka, *Toxicol. Appl. Pharmacol.*, **18**, 743 (1971).

(3) M. A. Innis and I. P. Lee, *ibid.*, **22**, 304 (1976).

(4) C. T. Hardesty, N. A. Chaney, and J. A. R. Mead, *Cancer Res.*, **32**, 1884 (1972).

(5) R. I. Geran, N. H. Greenberg, M. M. McDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, **3**, 1 (1972).

(6) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975, p. 651.

(7) K. W. Kohn, M. J. Waring, D. Glaubiger, and C. A. Friedman, *Cancer Res.*, **35**, 71 (1975).

(8) A. Rahman, J. P. Davignon, and J. C. Cradock, *Proc. Am. Assoc. Cancer Res.*, **17**, 119 (1976).

(9) N. R. Bachur, A. L. Moore, J. G. Bernstein, and A. Liu, *Cancer Chemother. Rep.*, **54**, 89 (1970).

(10) N. R. Bachur, R. C. Hildebrand, and R. S. Jaenke, *J. Pharmacol. Exp. Ther.*, **191**, 331 (1974).

(11) W. I. Higuchi, *J. Pharm. Sci.*, **56**, 315 (1967).

(12) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975, p. 765.

(13) S. Agharkar, S. Lindenbaum, and T. Higuchi, *J. Pharm. Sci.*, **65**, 747 (1976).

(14) T. Higuchi and R. J. Kuramoto, *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 393 (1954).

(15) D. Guttman and T. Higuchi, *ibid.*, **45**, 659 (1956).

(16) M. Gibaldi and H. Weintraub, *J. Pharm. Sci.*, **57**, 832 (1968).

(17) A. T. Florence and A. Rahman, *J. Pharm. Pharmacol., Suppl.*, **27**, 55 (1975).

(18) A. T. Florence, P. H. Elworthy, and A. Rahman, *ibid.*, **25**, 779 (1973).

(19) A. P. Simonelli, S. C. Mehta, and W. I. Higuchi, *J. Pharm. Sci.*, **58**, 538 (1969).

(20) E. I. Stupak and T. R. Bates, *ibid.*, **61**, 400 (1972).

(21) *Ibid.*, **62**, 1806 (1973).

(22) O. I. Corrigan and R. F. Timoney, *J. Pharm. Pharmacol.*, **27**, 759 (1975).

(23) O. I. Corrigan, R. F. Timoney, and M. J. Whelan, *ibid.*, **28**, 703 (1976).

(24) A. P. Simonelli, "Report to the National Cancer Institute," Contract PH 43-68-1284, 1969.

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