< 0.05) at all but two of the sampling times. Nevertheless, significant differences were observed since actual differences exceeded 20%.

The relative standard deviation for the mean peak plasma concentration was <25%, and the number of subjects necessary to detect a 20% difference was 16–17. Statistically significant differences were observed for this parameter, since actual differences were >50%. Similarly, it would have taken >30 subjects to detect a 20% difference in time to reach peak plasma concentration. However, significant differences were observed because actual differences exceeded 200%. No significant differences were seen among the products for $AUC_{0-8\ hr}$ or $AUC_{0\to\infty}$, although the power of the study was adequate to detect differences of 14.5%.

There was a perfect rank-order correlation of the mean percent of drug dissolved at 5 min in both acid and water for products 2–6 and the propylthiouracil plasma concentration observed at 20 min. The best correlations were found between the mean percent dissolved in water at 5, 20, and 60 min and the plasma propylthiouracil concentration at 20 min, with correlation coefficients of 0.81, 0.86, and 0.89, respectively. Corresponding correlation coefficients of 0.82, 0.80, and 0.85 were found for dissolution data obtained in acid. Attempts to relate either peak plasma propylthiouracil concentration or time to peak concentration were less successful. Correlation coefficients describing peak concentration and any of the dissolution values were all <0.42. The best correlation with time to peak concentration was with the percent dissolved at 60 min in either water or acid ($r = 0.75$). It is apparent the results of the dissolution studies were not useful in providing generally applicable correlations with *in vivo* data. However product 2, which exhibited the longest time to achieve peak concentration, was somewhat more slowly dissolved in acid at each sampling time compared with the other more rapidly absorbed dosage forms.

REFERENCES

(1) A. Melander, E. Wahlin, K. Danielson, and A. Hanson, *Acta Med. Scand.*, **201**, 41 (1979).

(2) "Public Health Service, Approved Drug Products with Proposed Therapeutic Equivalence Evaluations," Food and Drug Administration, Rockville, Md., January 1979, p. 114.

(3) *Fed. Regist.*, **42**, January 7, 1977, p. 1649.

(4) *Anonymous*, *Statist. Bull. Metrop. Life Insur. Co.*, **58**, 1 (1977).

(5) E. G. Williams, *Aust. J. Sci. Res. A.*, **2**, 149 (1949).

(6) H. P. Ringhand and W. A. Ritschel, *J. Pharm. Sci.*, **68**, 1461 (1979).

(7) "The United States Pharmacopeia," 19th Rev., U.S. Pharmacopeial Convention, Rockville, Md., 1975, p. 423.

(8) Fourth Supplement to USP XIX and NF XIV. U.S. Pharmacopeial Convention, Inc., Rockville, Md., 1978, pp. 194–195.

(9) B. J. Winer, "Statistical Principles in Experimental Design," 2nd ed., McGraw-Hill, New York, N.Y., 1962, p. 452.

(10) B. J. Winer, "Statistical Principles in Experimental Design," 2nd ed., McGraw-Hill, New York, N.Y., 1962, p. 191.

Pharmacokinetic Profile of Intravenous Liposomal Triamcinolone Acetonide in the Rabbit

ISAAC ABRAHAM ˣ, JANE C. HILCHIE, and MICHAEL MEZEI

Received June 15, 1981, from the *College of Pharmacy, Dalhousie University, Halifax, Nova Scotia, Canada.* Accepted for publication October 8, 1982.

Abstract □ The pharmacokinetics of triamcinolone[2-^{14}C]acetonide, encapsulated in neutral multilamellar liposomes, and a control preparation of the steroid in a 3:1 solution of polyethylene glycol–water was investigated in the rabbit after single intravenous bolus injections. Blood samples were obtained at various times up to 7 hr postinjection and assayed for the drug by liquid scintillation counting. Blood drug concentration–time data showed biexponential decay and were analyzed by nonlinear, least-squares regression analysis to obtain the initial (time zero) drug concentration $[(C_b)_0]$ and the initial (fast, α) and terminal (slow, β) disposition rate constants. From these estimates the central compartment volume (V_c) and the respective half-lives $[(t_{1/2})_\alpha, (t_{1/2})_\beta]$ of the fast and slow disposition phases were calculated. The total body clearance (CL_T) and the apparent distribution volume (Vd) were obtained by nonparametric analysis. Significant differences were observed between the liposome-encapsulated dosage form and the solution of the steroid in β and Vd_β. While β for the liposomal form was smaller than that for the solution, the apparent Vd was larger with the liposome-encapsulated drug. There was no difference in the total body clearance of the drug in the two dosage forms. Results of the study suggest that when administered by the intravenous route, liposome-encapsulated drug may exhibit extensive tissue distribution and a prolonged half-life.

Keyphrases □ Triamcinolone acetonide—liposomal encapsulation, pharmacokinetics, rabbits □ Dosage forms—liposomal encapsulation, triamcinolone acetonide, pharmacokinetics, rabbits □ Pharmacokinetics—liposome-encapsulated triamcinolone acetonide, rabbits

In recent years liposomes—artificial phospholipid vesicles—have gained increasing attention as a potential drug delivery system (1). A common objective for the choice of liposomes as drug carriers is the desire to ensure selective distribution or localization of therapeutic agents in specific organ tissues (2–4). By this means, high concentrations of an agent in an organ of interest can be attained while reducing potential toxicity to other organs, which can result from indiscriminate dispersion of the agent in the body. Notable successes have been reported with liposomal preparations in the treatment of arthritic joints (3, 5) and experimental leishmaniasis (6) and in the alleviation of respiratory distress syndrome in infants (7). However, reports on the formal pharmacokinetic analyses of liposome-encapsulated drugs are rather scanty.

Unlike many drug delivery systems that are designed to release the active component (drug) instantly *in vivo*, the liposome-encapsulated dosage form in circulation may remain as a single phospholipid vesicle for relatively long periods. In this instance the pharmacokinetic behavior of the encapsulated drug will largely be determined by the disposition characteristics of the liposomal entity. Several physical and chemical factors of the liposome can, therefore, potentially influence the disposition of liposome-entrapped drug. Such factors include vesicle size, surface charge, and lipid composition.

As interest in the clinical application of liposomes as drug carriers grows, there is need to gain more information about the pharmacokinetics of drugs and, hence, their

0022-3549/83/1200-1412$01.00/0

therapeutic fate when entrapped in such phospholipid vesicles. The objective of the present study was to characterize the pharmacokinetics of a model compound, triamcinolone [2-^{14}C]acetonide, entrapped in neutral multilamellar liposomes after rapid intravenous injection in the rabbit.

EXPERIMENTAL

Liposomal Triamcinolone—Neutral, multilamellar liposomes containing triamcinolone[1], dipalmitoyl DL-α-phosphatidylcholine[2], and cholesterol[2] in the respective mole ratio of 0.5:1.1:0.5 were prepared as previously described (4). The volume of the final liposomal suspension was adjusted with the dispersion medium (8 m*M* $CaCl_2$) so that a 0.3-ml dose contained the desired radioactivity (12 μCi). Over 80% of the liposomes obtained by the procedure were shown by microscopic size distribution to have a mean diameter of 9 μm (range 7–11 μm) (8). Each batch of liposomes was used within 3 days of preparation, and daily microscopic examination of the liposomes showed no apparent lysis of the vesicles.

A control preparation of unencapsulated triamcinolone was prepared as a solution in polyethylene glycol 400–water (3:1) so that a 0.3-ml dose contained the desired radioactivity (12 μCi). The clear control solution of triamcinolone had approximately the same viscosity as the liposomal suspension as determined, visually, by their flow pattern.

Intravenous Administration of Liposomal and Control Triamcinolone Preparations—The hair on the ear lobes of male New Zealand White rabbits (3–4 kg) was removed with an animal hair clipper[3]. An infusion set[4] equipped with a 21-gauge (0.8-mm) hypodermic needle and a winged adapter was inserted into the central artery of one ear lobe to facilitate sampling of blood for drug analysis. The patency of the set was maintained by intermittent flushing with heparinized sodium chloride injection (100 IU/ml).

After removing 0.5 ml of arterial blood as a control sample, a single 0.3-ml dose of the triamcinolone preparation in a 1-ml tuberculin syringe[5] was administered by rapid intravenous injection *via* the marginal vein of the opposite ear lobe. Following administration of the dose, serial 0.5-ml blood samples were obtained over a 7-hr period *via* the catheterized ear artery. The blood samples were placed in glass tubes[6] containing 0.5 ml of citrated buffer solution as anticoagulant. The samples were frozen (−10°) until analyzed.

Quantitation of Triamcinolone in Whole Blood—Five milliliters of ethanol (95%) was added to the citrated blood (0.5 ml) in the stoppered collection tube. The mixture was vortexed at high speed for 2 min and centrifuged at 1000×*g* for 5 min at room temperature. The supernatant was decanted into a 50-ml Erlenmeyer flask, and the pellet was resuspended in another 5-ml aliquot of ethanol; the process was repeated four more times. The combined ethanolic extracts were evaporated to dryness over a boiling water bath. The residue was redissolved in 15 ml of methylene chloride and transferred to a 20-ml glass counting vial. The methylene chloride was allowed to evaporate to dryness overnight at room temperature. The residue was redissolved in 10 ml of Bray's solution[7], 0.5 ml of glacial acetic acid was added, and then the radioactivity was determined by liquid scintillation counting[8].

The blood triamcinolone concentration of each sample was calculated from the radioactivity and the specific activity of the administered preparation after correction for background values (determined using a blank). Over the triamcinolone concentration range of ~15–960 ng/ml, this extraction procedure resulted in ~80% recovery of equivalent radioactivity from whole blood spiked with the drug.

Data Analysis—Blood triamcinolone concentration (C_b) *versus* time (t) data after a single intravenous bolus injection were fitted to the following with the aid of the least-squares regression analysis program, NONLIN (9):

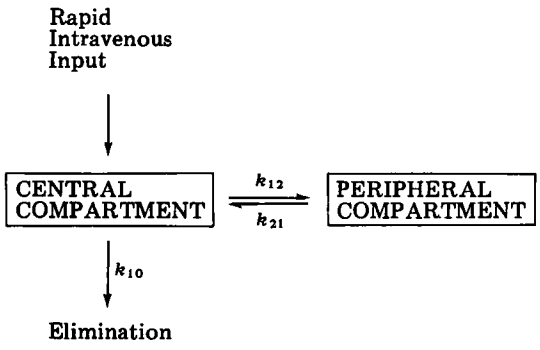

Figure 1—*A representation of the two-compartment open model system.*

$$C_b = Ae^{-\alpha t} + Be^{-\beta t} \quad \text{(Eq. 1)}$$

Initial estimates of A, B, α, and β were obtained with the CSTRIP program (10). In Eq. 1, α and β are first-order disposition rate constants, while A and B represent appropriate concentration constants. The two-compartment open model system with elimination from the central compartment (Fig. 1) was assumed.

The central compartment volume (V_c) was estimated by:

$$V_c = \text{Dose}/(C_b)_0 \quad \text{(Eq. 2)}$$

where $(C_b)_0 = (A + B)$. The intercompartmental transfer rate constants, k_{21} and k_{12}, and the elimination rate constant, k_{10}, were calculated from:

$$k_{21} = (A\beta + B\alpha)/(C_b)_0 \quad \text{(Eq. 3)}$$

$$k_{10} = \alpha\beta/k_{21} \quad \text{(Eq. 4)}$$

$$k_{12} = (\alpha + \beta) - (k_{21} + k_{10}) \quad \text{(Eq. 5)}$$

The total body clearance (CL_T) was calculated using:

$$CL_T = \frac{\text{Dose}}{\int_0^\infty C_b \cdot dt} \quad \text{(Eq. 6)}$$

where $\int_0^\infty C_b \cdot dt$ is the total area under the blood drug concentration–time curve and was estimated by the trapezoidal rule to obtain the area up to the last measured blood triamcinolone concentration (C_b^*). The area beyond C_b^* was computed by dividing C_b^* by β. The apparent volume of distribution (Vd_β) was determined by the relationship:

$$Vd_\beta = CL_T/\beta \quad \text{(Eq. 7)}$$

Half-life values for the fast disposition phase $(t_{1/2})_\alpha$ and terminal phase $(t_{1/2})_\beta$ were calculated using:

$$(t_{1/2})_\alpha = 0.693/\alpha \quad \text{(Eq. 8)}$$

$$(t_{1/2})_\beta = 0.693/\beta \quad \text{(Eq. 9)}$$

The unpaired, two-tailed Student's t test was used to assess the significance of the observed differences in the pharmacokinetic parameters between the control and liposomal triamcinolone preparations. A $p_{0.05}$ significance level was used.

RESULTS AND DISCUSSION

Figure 2 illustrates characteristic dose-normalized blood concentration–time curves for the control and liposomal triamcinolone dosage forms in two separate rabbits after single intravenous bolus injections. Relative to the control preparation, a characteristic feature of all liposomal curves was a more rapid initial disposition phase followed by a slower, more sustained terminal phase. A comparison of the mean pharmacokinetic constants (±*SEM*) for the control and liposomes is presented in Table I.

It has been reported (11) that triamcinolone hexacetonide administered orally to cats and dogs did not undergo significant deacetonization or de-esterification. Earlier in this laboratory it was determined that 90% of the intravenous dose of triamcinolone acetonide was excreted unchanged in the urine by rabbits (8). Recently we found that the total radioactivity of the ethanolic solution from whole blood obtained from

[1] New England Nuclear, Boston, Mass.
[2] Sigma Chemical Co., St. Louis, Mo.
[3] Oster, Milwaukee, Wis.
[4] Butterfly, Abbott Ireland Ltd., Sligo, Ireland.
[5] Plastipak, Becton, Dickinson & Co. Canada Ltd., Mississauga, Ont.
[6] Venoject, Kimble-Terumo, Elkton, Md.
[7] Bray's scintillation counting solution: Omnifluor (New England Nuclear, Boston, Mass.), 0.8 g; naphthalene, 6 g; ethylene glycol, 2 ml; methanol, 10 ml; and 1,4-dioxane to 100 ml.
[8] Beckman Spectrometer Model LS 3133T.

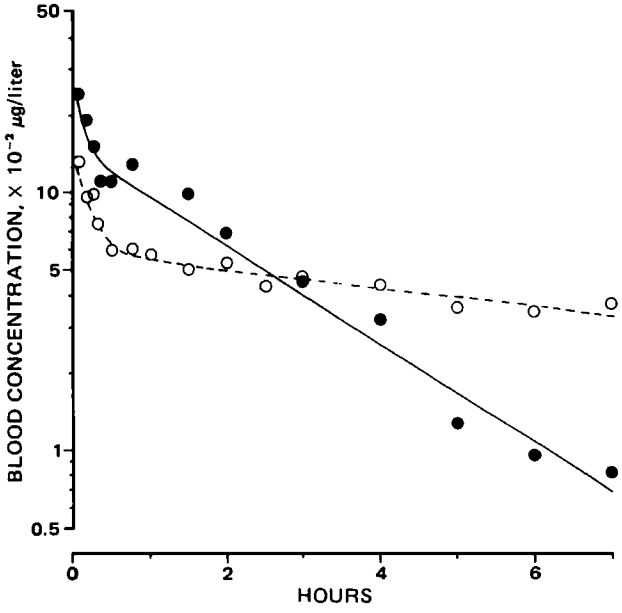

Figure 2—*Dose-normalized blood levels of triamcinolone following single intravenous bolus injections of control (●) and liposomal (○) preparations in two separate rabbits.*

rabbits receiving intravenous triamcinolone was comparable with the radioactivity determined after the ethanolic solution was subjected to ethyl acetate extraction of the intact drug. These findings indicate that the ^{14}C-label on the ketal ring of triamcinolone acetonide is a stable tracer for disposition studies. They also suggest that the total radioactivity of the ethanolic solution from whole blood represented, essentially, the unchanged drug.

Compared with the control, the overall apparent distribution of triamcinolone in the liposomal form was more extensive. On the average, V_c increased by (1.8 − 0.7) liter/kg = 1.1 liter/kg (Table I), while Vd_β changed by (7.09 − 1.41) liter/kg = 5.68 liter/kg when the liposomal form of the drug was used. These volume increases suggest that, within both the central and peripheral compartments, liposome-entrapped drug reached organ tissues that were not normally accessible to the unencapsulated triamcinolone. It has been observed (12) that in plasma and other calcium-containing media, negatively charged liposomes aggregate to form larger particles; these particles are then rapidly removed from the circulatory system by the reticuloendothelial system (RES), of which the liver and spleen are major components. It has also been reported that subfractionation of livers of animals receiving liposomes showed that liposome-entrapped enzymes were localized chiefly in the lysosomal fraction (13). It is thus apparent that cells of the RES, particularly the Kupffer cells in the liver, play a major role in the removal of liposomes from the circulatory system, although electron microscopic evidence also indicates that hepatic parenchymal cells may be involved in liposomal clearance (14). A two-stage mechanism for liposomal removal from circulatory system has been proposed (15, 16) in which the Kupffer cells are thought to be responsible for the rapid phase of liposomal removal from the blood while the slower disappearance phase is attributable to the liver parenchymal cells. Therefore, it may be deduced that the liver and spleen could be regarded as part of the central compartment because of their high vascularity, ease of blood perfusion, and relatively high content of Kupffer cells. In addition, the liver parenchyma could be considered as part of the peripheral compartment.

The increase in the apparent volume of distribution with the liposomes and the concomitant increase in α and k_{12} relative to the control dosage form (Table I) suggest that liposomes potentially increase the rate and extent of entrapped drug distribution relative to the unencapsulated form of the drug. The relative constancy of the liposomal curve terminal slope (Fig. 2) suggests that any rapid initial accumulation of liposomes in the liver and other organs of the RES does not result in significant lysis of the vesicles. Since the liver does not metabolize triamcinolone as such (8, 11), any significant lysis of liposomes in the liver and subsequent release of drug would have resulted in a change in the slope of the terminal portion of the liposomal curve, which would then have declined in a fashion somewhat parallel to the terminal portion of the control curve. It is possible that the majority of liposomes (particularly the smaller vesicles) accumulating in the liver were held in the relatively open and fenestrated endothelium of the liver capillaries (1). It is not unlikely for small intact liposomes held in this type of hepatic vasculature architecture to reenter the circulatory system and sustain triamcinolone levels. Assuming that they do accumulate rapidly in the liver and are able to reenter the circulatory system liposomes could prove beneficial not only as drug carriers for targeting the liver and other organ tissues of the RES with therapeutic agents, but also as a potential intravascular depot system.

There was no significant difference in the mean clearances (0.73 ± 0.17 and 0.57 ± 0.06 liter/hr/kg, respectively) of triamcinolone from the liposomal and solution dosage forms. From the relationship between CL_T, Vd_β and β (Eq. 7), it is seen that an increase in Vd_β and a concurrent decrease in β tend to offset each other and thereby minimize potential changes in CL_T. However the apparent similarity of CL_T values observed in this study underlie the fact that there may not be a fundamental change in the clearance mechanisms of triamcinolone in the rabbit whether the steroid is administered in the liposomal or solution form. Similarities in the k_{10} (Table I) tend to support this view.

Due to technical difficulties it was not possible to administer equal amounts of triamcinolone in the two dosage forms. In the control studies, two of the doses employed were 263 and 803 µg. At these dose levels the respective areas under the blood drug concentration–time curves were 200 and 579 µg/hr/liter; CL_T values were 0.44 and 0.42 liter/hr/kg; and β values were 0.34 and 0.42 hr^{-1}, respectively. These etimates do not indicate that triamcinolone *per se* exhibits dose-dependent pharmacokinetics in the rabbit over the dose range employed in this study. It is, therefore, doubtful that the observed differences in the pharmacokinetics were due to differences in the dose administered in the two dosage forms.

Probably an ideal control dosage form in this study would have been a physical admixture of all the components in the liposomal dosage form, *i.e.* triamcinolone, phospholipids, cholesterol, and the dispersing liquid (8 m*M* aqueous calcium chloride). However, triamcinolone is insoluble in aqueous media; a control preparation which might contain triamcinolone crystals would be unsuitable for intravenous administration. Moreover, the presence of drug crystals in the control raises another

Table I—Mean Pharmacokinetic Parameters for Control and Liposomal Triamcinolone after Single Intravenous Injections in the Rabbit

Parameter	Mean (± *SEM*) Control[a]	Mean (± *SEM*) Liposomal[b]	*t* Test[c]	Significance Level
Dose, µg	769 (128.80)	314 (26.12)	—	—
$(C_b)_0$, µg/liter	326.83 (55.8)	365 (13.76)	—	—
α, hr^{-1}	9.22 (4.36)	17.57 (5.01)	1.575	NS[d]
β, hr^{-1}	0.41 (0.04)	0.13 (0.03)	5.754	$p < 0.001$
$(t_{1/2})_\alpha$, hr	0.23 (0.09)	0.07 (0.02)	1.879	NS
$(t_{1/2})_\beta$, hr	1.72 (0.14)	9.03 (3.35)	1.964	NS
V_c, liter/kg	0.70 (0.06)	1.80 (0.57)	1.722	NS
Vd_β, liter·kg	1.41 (0.16)	7.09 (1.88)	2.715	$p < 0.005$
k_{21}, hr^{-1}	3.48 (1.19)	3.14 (0.39)	0.292	NS
k_{12}, hr^{-1}	5.30 (3.20)	13.76 (4.52)	1.487	NS
k_{10}, hr^{-1}	0.86 (0.14)	0.78 (0.27)	0.249	NS
CL_T, liter/hr/kg	0.57 (0.06)	0.73 (0.17)	0.822	NS

[a] $n = 5$; [b] $n = 6$. [c] Critical $t_{0.05} = 2.262$. [d] NS—not significant at $p_{0.05}$.

objection in that the drug may not be presented in the same physical state, since in the liposomal triamcinolone is present as a molecular dispersion in lipid micelles (17). Under these circumstances the possibility of a dissolution-dependent disposition of triamcinolone in the control preparation would seriously affect the pharmacokinetic comparison of the two dosage forms. Finally, a physical admixture of drug, lipids, and calcium chloride solution could, potentially, promote the spontaneous formation of an undetermined number of liposomes when agitated. If this happened, the control would not be totally free of drug-containing liposomes. Thus, while the triamcinolone solution in polyethylene glycol–water used in this study may not be qualitatively similar to the liposomal dosage form, it was designed to present the model compound in an intravenous dosage form that was miscible with plasma water. The comparison of the pharmacokinetics of triamcinolone in liposomal and solution dosage forms is, thus, analogous to other comparative studies (*e.g.*, bioavailability) of a therapeutic agent in different formulations which may not (and often do not) contain the same excipients. If it is assumed that the presence in blood of exogenous lipids (used in the preparation of the liposomes) and polyethylene glycol in the concentrations used did not influence blood flow rate significantly, then the differences in β and Vd_β observed in this study are due probably to the favorable physicochemical properties (especially lipid solubility) of the liposomal entity.

Results of the present study indicate that liposome-encapsulated triamcinolone enhances tissue distribution of the drug in the rabbit. The results also suggest that, given by the intravenous route, neutral multilamellar liposomes could serve as carriers for chemotherapeutic agents whose efficacy depends on sustained blood levels and deep tissue distribution.

REFERENCES

(1) R. L. Juliano and D. Layton, in "Drug Delivery Systems," R. L. Juliano, Ed., Oxford University Press, New York, N.Y., 1980, chap. 6.

(2) Y. E. Rahman, E. A. Cerny, S. L. Tollakson, B. J. Wright, S. L. Nance, and J. F. Thompson, *Proc. Soc. Exp. Biol. Med.*, **146**, 1173 (1974).

(3) M. M. Jonah, E. A. Cerny, and Y. E. Rahman, *Biochim. Biophys. Acta*, **541**, 321 (1978).

(4) M. Mezei and V. Gulasekharam, *Life Sci.*, **26**, 1473 (1980).

(5) N. C. Phillips, D. P. Page Thomas, C. G. Knight, and J. T. Dingle, *Ann. Rheum. Dis.*, **38**, 535 (1979).

(6) C. A. Alving, E. A. Steck, W. L. Hanson, P. S. Loizeaux, W. L. Chapman, Jr., and V. B. Waits, *Life Sci.*, **22**, 1021 (1978).

(7) H. Ivey, S. Roth, and J. Kattwinkel, *Pediatr. Res.*, **11**, 573 (1977).

(8) V. Gulaskharam, "Liposomes for Selective Delivery of Drugs in Topical Routes of Administration." Master of Science thesis, Dalhousie University, Halifax, Nova Scotia, 1980.

(9) C. M. Metzler, G. L. Elfring, and A. J. McEwen, *Biometrics*, **30**, 562 (1974).

(10) A. J. Sedman and J. G. Wagner, *J. Pharm. Sci.*, **65**, 1006 (1976).

(11) V. Zbinovsky and P. Chrekian, in "Analytical Drug Profiles," Vol. 6, K. Florey, Ed., Academic, New York, N.Y., 1977, pp. 579–598.

(12) R. L. Juliano and D. Stamp, *Biochem. Biophys. Res. Commun.*, **63**, 651 (1975).

(13) G. Gregoriadis and B. E. Ryman, *Biochem. J.*, **129**, 123 (1972).

(14) Y. E. Rahman and B. J. Wright, *J. Cell Biol.*, **65**, 112 (1975).

(15) G. Gregoriadis and D. E. Neerunjun, *Eur. J. Biochem.*, **47**, 179 (1974).

(16) G. Sherphof, F. Roerdink, M. Waite, and J. Parks, *Biochim. Biophys. Acta*, **542**, 296 (1978).

(17) F. J. T. Fildes and J. E. Oliver, *J. Pharm. Pharmacol.*, **30**, 337 (1978).

ACKNOWLEDGMENTS

This project was supported by the Medical Research Council of Canada (Grant MA 6664).

The authors are particularly grateful to Dr. C. T. Ueda and Mrs. Jeannetta G. Nickols, University of Nebraska Medical Center, for the use of their computer facilities, Mrs. Anne Fenton of the Dalhousie University Animal Care Facility for her technical assistance, and Mrs. Annette Cook for her excellent secretarial work.

Acrylic Microspheres *In Vivo* IX: Blood Elimination Kinetics and Organ Distribution of Microparticles with Different Surface Characteristics

PER ARTURSON ‡, TIMO LAAKSO *, and PETER EDMAN *x

Received May 10, 1982, from the **Division of Pharmacy, Department of Drugs, National Board of Health and Welfare, S-751 25 Uppsala, Sweden* and ‡*Department of Pharmaceutical Biochemistry, Biomedical Center, University of Uppsala, S-751 23 Uppsala, Sweden.* Accepted for publication September 24, 1982.

Abstract □ The elimination of microparticles from blood after intravenous injection is dependent on the surface characteristics of the particles. The half-life in blood increases from 44 to 84 min after modification of surface-localized human serum albumin with polyethylene glycol. Irrespective of the surface properties, particles are localized in the reticuloendothelial system, mainly in the liver and spleen. In preimmunized mice, the distribution of particles is somewhat altered, *i.e.*, the liver and lung uptake is significantly higher in preimmunized animals than in untreated animals. The rate of phagocytosis of particles with different surface characteristics has also been studied *in vitro* with isolated mouse peritoneal macrophages. This technique gives a good correlation with the *in vivo* results; thus particles with a short half-life in mice are rapidly phagocytosed by the macrophages *in vitro*.

Keyphrases □ Microparticles—polyacrylamide, blood elimination kinetics, organ distribution, effect of surface characteristics, mice □ Elimination—polyacrylamide microparticles from blood, kinetics, organ distribution, effect of surface characteristics, mice □ Delivery systems—polyacrylamide microparticles, blood elimination, kinetics, organ distribution, mice

Immobilized systems in the form of small beads or particles have recently been introduced as carriers of enzymes *in vivo* (1). Some of these systems are characterized as biodegradable (*e.g.*, liposomes), while others are slowly metabolized (*e.g.*, acrylic particles). Irrespective of the type of particles, these systems show great promise as a tool for "active targeting" of enzymes and other macromolecules to specific cells or organs in the body. However, one of the

0022-3549/83/1200-1415$01.00/0