Drug Binding by Reservoirs in Elastomeric Infusion Devices

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Received October 27, 1993; accepted January 25, 1994

Drug binding by an elastomeric infusion device reservoir was assessed by measuring its ability to bind fifteen model solutes. Octanol/water (o/w) and hexane/water (h/w) partition coefficients were regressed against the reservoir's solute equilibrium binding constant to generate a binding model. The reservoir's drug binding ability was calculated with the model and drug partition coefficients, which were determined for seventeen commonly infused drugs including tobramycin, gentamicin, penicillin G, piperacillin, lidocaine, morphine, ceftriaxone, imipenem-cilastatin, amphotericin B, ticarcillin and clavulanate, pentamidine, vancomycin, foscarnet, desferoxamine, acyclovir, fluconazole and vinblastine. Formulations studied included 0.9% Saline and 5% Dextrose. With the exception of lidocaine, imipenem, vinblastine and fluconazole, octanol/formulation and hexane/formulation partition coefficients were too low to be measured for these drugs. Thus, the majority of the drugs, when reconstituted in 0.9% Saline or 5% Dextrose, will not be bound by the reservoirs. The magnitude of drug loss for the most highly bound species, fluconazole, is less than 2%. Therefore the reservoirs used in this study are essentially inert with respect to binding of the drugs evaluated in this study.

KEY WORDS: elastomeric reservoirs; drug binding; drug compatibility; partition coefficients.

INTRODUCTION.

A pharmaceutical formulation must be physicochemically compatible with its container. Container-product compatibility is impacted by several processes including the container's ability to bind product components. The container impacts product utility if it binds either the active ingredient (lowering its availability), or a formulation stabilizer (impacting product stability).

Drug binding can be modeled using fundamental properties of the drugs and container material. Such a model establishes the maximal equilibrium binding of the drug and delineates the potential that a product/container system will fail. A model would be useful in terms of comparing the performance of two or more potential container materials or in comparing a current versus a new material.

Elastomeric infusion devices contain a plastic reservoir in which the drug formulation is stored and delivered. In this study the drug binding properties of a rubber reservoir was modeled and the model was used to assess the reservoir's compatibility with seventeen drugs commonly dispensed by infusion devices.

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MATERIALS AND METHODS.

Partition Coefficients, Model Solutes.

Materials. Model solutes used are summarized in Table I. The solutes were reagent grade with purities of 97% or higher.

Interaction Methods. Octanol-water ($P_{o\text{-}w}$) and hexane-water ($P_{h\text{-}w}$) partition coefficients were determined by shake flask methods. Aqueous donor solutions containing model solutes were contacted with the organic solvent with gently stirring for 24 hours at ambient temperature. The composition of the partitioning chambers was optimized for each solute so that the difference between its initial and equilibrium concentration could be readily measured. After equilibration, the phases were separated and the solute remaining in the donor solution measured. Duplicate test articles were prepared for each model solute and solvent.

Analytical. Solute concentration was determined by reversed phase HPLC using two point standard curves spanning an order of magnitude of analyte concentration (Table II). The high end of this range was the donor solution's initial concentration.

Binding Model.

Materials. A production lot of natural rubber infusion reservoirs was used along with the model solutes from Table I.

Interaction Methods. Composite aqueous donor solutions containing three model solutes were used. Model solutes were grouped to facilitate their quantitation (Table I). Duplicate test articles were prepared by contacting portions of the reservoir with 50 mL of donor solution in glass bottles. Control solutions were similarly prepared but without reservoirs. The reservoir mass and initial solute concentration in the donor solution were optimized to ensure that sufficient solute remained in solution after equilibrium to be measured accurately. In general, the solute concentration was between 30 and 100 ppm while the reservoir weight was between 1.0 and 2.5 grams.

Water was the donor matrix for the uncharged model solute composites. The other composites (B, D and E from Table I) were acidified with HCl to ensure the protonation of the ionic solutes.

Test and control articles were stored for ~2 weeks at 35°C with constant gentle agitation. After equilibration, an aliquot of the donor phase was analyzed for remaining analyte by HPLC. The control solutions served as analytical standards.

Analytical Methods. In general, the HPLC methods used to analyze the binding samples were the same as those used for the partition coefficients. In several cases, however, analytical interferences required modified analytical conditions.

Binding Model. The reservoir's binding model is obtained by regressing the solute's equilibrium binding constants versus their log $p_{o/f}$ and log $P_{h/f}$. A multiple linear regression analysis was used.

0724-8741/94/0700-0984$07.00/0

Table I. Model Solutes used in The Binding Experiments.

Name	Abbreviation	log $P_{o/w}$	log $P_{h/w}$	log E_b
Test Mixture A.				
Dimethyl phthalate	DMP	1.57	0.76	−2.21
Diethyl phthalate	DEP	2.44	1.85	−1.21
Dipropyl phthalate	DPP	3.42	3.07	−0.28
Test Mixture B.				
4-methylbenzoic acid (p-toulic acid)	MBH	2.39 (2.27,2.32)	−0.35	−2.60
4-ethylbenzoic acid	EBH	2.89	0.40	−1.83
4-tert-butylbenzoic acid	BBH	3.80	1.78	−1.03
Test Mixture C.				
Aniline	AN	0.93 (0.94)	−0.08 (−0.05)	−2.51
Acetanalide	AD	1.18 (1.16)	−1.88	−3.33
Diphenylguandine	DPG	−0.10	NA	NA
Test Mixture D.				
Ethyl-4-aminobenzoate	ETBZ	1.53 (2.57)	−0.36 (−0.01)	−2.51
Butyl-4-aminobenzoate	BUBZ	2.56	0.65 (1.43)	−1.50
Carbazole	CAR	3.58	1.88	−0.77
Test Mixture E.				
4-methylbenzyl alcohol	MBOH	1.63 (1.59)	−0.10	−2.62
ethyl paraben (1)	ETPB	2.50 (2.47)	−0.87 (−0.51)	−2.59
butyl paraben (1)	BTPB	3.43 (3.57)	0.39	−1.44

(1) hydroxybenzoic acid, − ester
NA = not applicable, could not be measured accurately.
Data in () are values reported in literature references 15 and 16.

Partition Coefficients, Drug Substances.

Materials. Drugs used are listed in Table III. In most cases, the materials were pharmaceutical vial products, reconstituted per the package insert and diluted to the appropriate concentration. For morphine and vinblastine, drug raw materials were used. For fluconazole, a commercially available pre-mixed product was used.

Interaction Methods. Drug formulations were prepared per Table III. Formulation pH was measured and 15 mL of the formulation was pipetted into four glass bottles. 30 mL of octanol or 50 mL of hexane was added to two of the bottles. The samples were stirred at ambient temperature for 24 hours and aliquots of the aqueous layer were retrieved and analyzed.

Analytical Methods. Formulation pH was measured ei-

Table II. Analytical Conditions, Model Solutes.

Mixture	Column	Mobile Phase	Flow Rate (mL/min)	Detection Wavelength (nm)
A	#1	60/40 MeCN/H_2O	1.0	228
B	#2	8/12 MeCN/0.1M phosphate buffer (pH 2.7)	0.8	215
C	#1	25/75 MeCn/0.1 M ammonium acetate	0.7	225
D	#3	60/140 MeCN/0.1% TEA (pH 2.7)	0.7	215
E	all conditions used are the same as Mixture B			

Notes: MeCn = acetonitrile, TEA = triethylamine. The various columns are: #1: Alltech (Deerfield, IL) Adsorbosphere C18 HS, 100 by 4.6 mm, 3μ particles, #2: Alltech Adsorbosphere C18, 100 by 4.6, 3μ particles, #3: Dupont Zorbax TMS, 150 by 4.6mm, 5μ particles. In most cases, the injection volume was 10 μL.

Table III. Drug Substances Used in this Study.

Name	Vendor	Conc. (mg/mL)
Tobramycin Sulfate, Nebcin®	Lilly	0.8
Gentamycin Sulfate	Lek Yugoslawia	0.6
Penicillin G Potassium, Pfizerpen®	Pfizer	40,000 (c)
Piperacillin Sodium, Piperacil®	Lederle	16
Lidocaine hydrochloride	Lyphomed	4
Morphine Sulfate pentahydrate	USP RS	0.5
Ceftriaxone	Hofmann-LaRoche	10
Imipenem-Cilastatin (Primaxin® IV)	Merck, Sharpe & Dohme	5
Amphotericin B for Injection USP	Lyphomed	0.25
Ticarcillin Sodium and Clavulanate Potassium, Timentin®	Beecham	15
Pentamidine isethionate, Pentam® 300	Fujisawa USA	3 (a)
Vancomycin hydrochloride, Vancocin®	Lilly	10
Foscarnet Sodium, Foscovir®	Abbott	24
Desferoxamine mesylate, Desferal®	Ciba-Geigy	5
Acyclovir Sodium, Zovirax®	Burroughs Wellcome	5
Fluconazole, Diflucan® (b)	Pfizer	2
Vinblastine Sulfate	Aldrich	0.2

Note: Formulations prepared in both 0.9% NaCl and 5% (w/v) Dextrose (hydrous) at the same concentration except the following:

(a) This is the concentration in the D5W formulation. The concentration in the NS formulation was 2 mg/mL due to solubility limitations.

(b) obtained as Fluconazole Injection in iso-osmotic sodium chloride diluent in VIAFLEX® (Baxter, Deerfield, IL) plastic containers.

(c) concentration units are units/mL

ther directly (NaCl) or after ionic strength adjustment (dextrose). Residual drug concentrations were determined by HPLC methods (1–9), as validated internal methods (Table IV), or, for Foscarnet, were developed for this application. Ampotericin B was determined by UV spectroscopy (10). Analyte response was standardized against the analytical response obtained from the untreated formulation stock.

Materials.

The octanol and hexane were chromatographic grade. The chemicals used in the formulation diluents, samples, and analytical solutions were reagent grade.

RESULTS AND DISCUSSION.

Theoretical.

Solute uptake by a container is essentially a partition-mediated process. Maximum drug sorption occurs when the container and formulation equilibrate. An equilibrium constant, or partition coefficient, reflects the relative affinity of the solute for the two phases.

A drug's partition coefficient is the ratio of the equilibrium concentrations of the drug in the container and formulation phases:

$$P_{c/f} = C_c/C_f \quad (1)$$

A container-related partition coefficient can be measured directly or calculated from fundamental properties of the solute via a partition model based on a surrogate solvent. In the model approach, an organic solvent system is defined which mimics the binding behavior of the container. The model solute's partitioning behavior with the container and in the model solvents are determined, and an equation is derived to relate the corresponding partition coefficients. The drug's solvent-formulation partition coefficients are determined and the drug's container/formulation partition coefficient can be calculated with the use of this equation.

An appropriate binding model utilizes a solute's octanol-formulation (o/f) and hexane-formulation (h/f) partition coefficients: (11,12)

$$\log P_{c/f} = a(\log P_{o/f}) + b(\log P_{h/f}) + C \quad (2)$$

where a, b and c are linear regression curve fit coefficients.

The equilibrium binding constant (E_b) is defined as:

$$E_b = (m_c/W_c)/(m_f/V_f) \quad (3)$$

where m = the mass of the solute in a phase at equilibrium,
W = container weight (in grams),
V = the formulation volume (in liters), and
c and f refer to the container and the formulation.

E_b is analogous to $P_{c/f}$, differing as a gravimetric, versus a volumetric, expression of the solute's container concentration. E_b is easier to use since one usually knows a container material's weight and not its volume. Thus E_b can replace $P_{c/f}$ in equation 2.

The fraction of a formulation component which will be bound by a container (F_b) relates the solute's E_b, the formulation's volume (V_f) and the container's weight (W_c) as follows (13):

$$F_b = W_cE_b/(V_f + W_cE_b) \quad (4)$$

Table IV. Analytical Methods for Drugs, Baxter Internal Procedure Specifications.

Drug	Mobile Phase	Column	Detection
Tobramycin	H_2O/MeCN (85/15) (28.6 g/L Na_2SO_4, 4 g/L sodium octane sulfonate, 0.1% acetic acid)	Whatman Partsil ODS3, 250 by 4.6 mm, 5μ particles	Fluorescence Emission λ, 428 nm
Gentamicin	H_2O/MeOH (89/11) (28.6 g/L Na_2SO_4, 4g/L sodium hexane sulfonate, 0.1% acetic acid)	Hibar Lichrosorb RP8, 250 by 3.9 mm, 5μ particles	Fluorescence Emission λ, 428 nm
Pencillin G	45/55 MeOH/KH_2PO_4 buffer (pH 4.15)	Partisil RACII 50DS3, 100 by 4.6 mm, 5μ	UV, 225 nm
Lidocaine	1% formic acid, 1% dicyclohexylamine in water	Waters μBondapak C18, 300 by 3.9 mm, 10μ	UV, 254 nm
Primaxin®	4% MeOH/86% H_2O/10% 0.1M 3-[N-morpholino]propane sulfonic acid (pH 7)	Alltech Adsorbosphere C8, 150 by 4.6 mm, 5 μ particles	UV, 245 nm
Timentin®	7/93 MeCN/0.1 M sodium phosphate monobasic buffer	Alltech Licrosorb RP18, 250 by 4.6 mm, 5μ	UV, 230 nm
Vancomycin	920/70/10 0.2% triethylphosphate buffer/MeCN/Tetrahydrofuran	Beckman Ultrasphere ODS, 150 by 4.6 mm, 5μ particles	UV, 280 nm
Foscarnet	0.625 mL nitric acid, 0.4 g/L potassium hydrogen phthalate	Waters Ionpak Anion	UV, 290 nm (indirect)
Fluconazole	1000/285/145 sodium acetate buffer (pH 5)/MeOH/MeCN	Novapak C18, 150 by 4.6 mm, 5μ	UV, 261nm

Notes: MeCN = acetonitrile, MeOH = methanol

Partition Coefficients, Model Solutes.

The model solute's solvent/water partition coefficients are summarized in Table I. These data represent the mean of replicate determinations which typically agreed to within ±0.05 log units.

The model solutes chosen span a wide range in terms of their affinity for an organic phase. Solutes such as aniline (AN) have little affinity for the organic phase and would tend to remain in the formulation. Alternatively, solutes such as dipropyl phthalate (DPP) would be almost entirely bound by the organic phase (container). Thus the model solutes chosen for this application are well suited to a drug compatibility evaluation.

The measured partition coefficients agree well with published values. The difference between the measured and published data is typically less than 0.2 log unit (Table I), well within the variation associated with partition coefficient determinations (14). Major differences occur with the aminobenzoates (ETBZ and BUBZ) and most probably reflect the impact of pH on the partition coefficient for these ionizable solutes.

The Binding Model.

Measured E_b values for the model solutes are summarized in Table I. A material's binding model relates the solute's solvent/water partition coefficients and their E_b (Equation 3) via a multiple linear regression analysis with E_b as the dependent variable. The binding model for the reservoir is:

$$\log E_b = 0.31(\log P_{o/f}) + 0.48(\log P_{h/f}) - 2.88$$

where the standard errors associated with the curve fit coefficients are 0.06, 0.05 and 0.17 respectively and the correlation coefficient (r^2) is 0.966.

Figure 1 depicts the reservoir's binding model. The model exhibits no significant compound class bias and adequately reflects the behavior of all the model solutes. Thus the model is applicable for a wide range of aqueous species, including drug substances in pharmaceutical formulations.

Partition, Coefficients, Drug Substances.

The drug substances examined all possess ionizable functional groups. This is significant since the drug's affinity for an organic phase (e.g., container) is influenced by its charge state, which is impacted by the drug's pK_a and formulation pH.

Table V shows the pH of the drug formulations and,

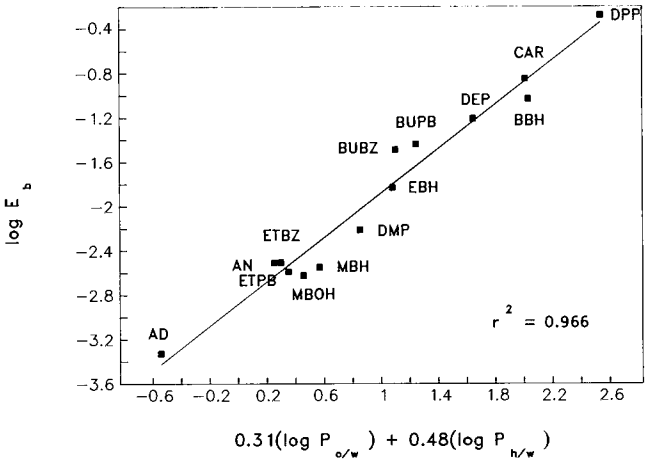

Figure 1. Binding Model for the Reservoir; The Relationship between the Model Solute's Equilibrium Binding Constant (E_b) and Partition Coefficients (P) [octanol/water (o/w) and hexane/water (h/w)].

Table V. Comparison of Formulation pH and Drug pK_a.

Drug	Formulation pH: 0.9% NaCl	Formulation pH: 5% Dextrose	pK_a	Reference
Tobramycin	6.36	6.36	NA	—
Gentamycin	4.50	4.64	7.9, 8.2	17
Penicillin G	6.53	6.45	2.8	18
Piperacillin	5.55	5.41	NA	—
Lidocaine	6.12	6.32	7.8	19
Morphine	5.23	5.47	6.5, 9.9	20
Ceftriaxone	5.77	5.79	3, 3.2, 5	21
Imipenen	NM	7.02	3.2, 9.9	22
Amphotericin B	NM	7.20	5.7, 10	23
Ticarcillin	6.18	6.12	NA	—
Pentamidine	5.25	5.42	NA	—
Vancomycin	3.64	3.65	NA	—
Foscarnet	7.32	NM	0.5, 3.4, 7.3	24
Desferoximine	4.48	4.49	NA	—
Acyclovir	10.76	10.19	NA	—
Fluconazole	4.91	NM	NA	—
Vinblastine	4.93	NM	5, 7	25

NM = not made; NA = not available

where available, their dissociation constant(s). Clearly, the drugs are formulated in primarily their charged (non-binding) form. The high formulation solubility of those drugs whose pK_a's were not available suggests that they are also ionized. Thus it was anticipated that the drug's partition coefficients would be low and the volume ratio used in the partition experiments was adjusted to maximize the ability to measure small partition coefficients.

A 10% change in an analyte's concentration in the donor solution (due to partitioning into the organic phase) is the minimum concentration change that is detected reproducibly. Thus, the minimum detectable log $P_{o/f}$ and log $P_{h/f}$ are -1.3 and -1.5.

As anticipated, log $P_{o/f}$ and log $P_{h/f}$ could not be measured for several drugs, as their partition coefficients were less than or equal to the minimum values. These drugs include: tobramycin, gentamicin, penicillin G, piperacillin, morphine, ceftriaxone, amphotericin B, Timentin® (ticarcillin and clavulanate), pentamidine, vancomycin, foscarnet, desferoxamine and acyclovir. The log $P_{o/f}$ for lidocaine in 0.9% NaCl was -1.05 and $P_{h/w}$ could not be measured. In the Primaxin® formulation, log $P_{o/f}$ and log $P_{h/f}$ for imipenem was measured at -1.27 and -1.28 respectively, while no partition coefficients could be measured for cilastatin. Vinblastine had a log $P_{o/f}$ of 0.29 in 0.9% NaCl and its log $P_{h/w}$ was not measurable. Similarly, fluconazole had a log $P_{o/f}$ in 0.9% NaCl of 0.45 while its log $P_{h/f}$ could not be measured.

Compatibility Assessment.

The fractional drug binding by the reservoir can be determined via equation 4. The upper 95% confidence level of the reservoir weight, obtained by weighing 15 randomly chosen reservoirs, was 5.93 grams and the fill volume was 100 mL. To determine the extent of the reservoir's drug binding, the drug's partition coefficients are substituted into equation 3 to obtain log E_b, which for the drug with the largest measured partition coefficients (fluconazole), is -3.42. This E_b, coupled with the reservoir weight and formulation volume, is substituted into equation 4 to obtain the fraction of fluconazole bound by the reservoir. The calculated F_b is 0.02 and thus the reservoir will bind 2% of the drug. For the other drugs tested, the maximal fractional binding is significantly less than 1% One observes, then, that the reservoir studied is essentially inert with respect to binding of the drugs examined herein.

This approach could be used to assess the reservoir's compatibility for any drug, with respect to drug binding alone, presuming that the drug's partition coefficients were known.

REFERENCES.

1. *The United States Pharmacopeia, XXII* (USP Pharmacopeial Convention, Rockville, Maryland, 1990), "Sterile Piperacillin Sodium", pp. 1088–9.
2. *USP XXII* (ibid), "Morphine Sulfate Injection", pp. 906–7.
3. *USP XXII* (ibid), "Sterile Ceftriaxone Sodium", pp. 257–8.
4. C. M. Dickinson, T. R. Navin and F. G. Churchill, "High Performance Liquid Chromatographic Method for Quantitation of Pentamidine in Blood Serum", *J. Chromatogr.*, 345:91–97 (1985).
5. S. Venkataram and Y.E. Rahman, "High Performance Liquid Chromatographic Analysis of Desferrioxamine using a Metal Free System", *J. Chromatogr.*, 411:494–497 (1987).
6. S. M. Cramer, B. Nathanael and C. Horvath, "High Performance Liquid Chromatography of Desferoxamine and Ferrioxamine: Interference by Iron Present in the Chromatography System", *J. Chromatogr.*, 295:405–411 (1984).
7. J. D. Glennon and A. T. Senior, "Simultaneous Determination of Desferioxamine and Ferrioxamine by High Performance Liquid Chromatography with Amperometric Detection", *J. Chromatogr.*, 527:481–489 (1990).
8. G. Land and A. Bye, "Simple High Performance Liquid Chromatographic Method for the Analysis of 9-(2-hydroxy-ethoxymethyl)quanine (Acyclovir)", *J. Chromatogr.*, 224:51–58 (1981).
9. *USP XXII*, Ibid, "Vinblastine Sulfate", pp. 1447–8.
10. *Analytical Profiles of Drug Substances, Vol. 6* (K. Florey, Ed., Academic Press, New York, 1977); "Amphotericin B", pp. 15.
11. D. R. Jenke, R. A. Kenley and D. S. Hayward, "Interactions between polymeric containers and their contained solution: Modeling of polymer-water solute partitioning via coupled solvent-water partition coefficients", *J. Appl. Poly. Sci.*, 43:1475–1482 (1991).
12. D. S. Hayward and D. R. Jenke, "Interactions between polymer containers and parenteral solutions: Correlating polymer-water interaction constants with solute partition coefficients", *Int. J. Pharm.*, 66:87–96 (1990).
13. R. A. Kenley and D. R. Jenke, "Determination of solute-polymer interaction properties and their application to parenteral product container compatibility evaluations", *Pharm. Res.*, 7:911–918 (1990).
14. J. C. Dearden and G/A. Bresnen, "The measurement of partition coefficients", *Quant. Struct. Act. Relat.*, 7:133–144 (1988).
15. A. Leo and C. Hansch, *Substituent Constants for Correlation Analysis in Chemistry and Biology* (J. Wiley, New York, 1979).
16. A. Leo, C. Hansch and D. Elkins, "Partition Coefficients", *Chem. Rev.*, 71:525–616 (1971).
17. B. E. Rosenkrantz, J. R. Greco, J. G. Hoogerheide and E. Moden, "Gentamicin Sulfate" in *Analytical Profiles of Drug Substances, Volume 9* (K. Florey, ed., Academic Press, New York, 1980) pp. 310.
18. J. Kirschbaum, "Penicillin G, Potassium", in *Analytical Profiles of Drug Substances, Volume 15* (ibid, 1986) pp. 462–4.
19. K. Groningsson, J.E. Lindaren, E. Lundberg, R. Sandberg and

A. Wahlen, "Lidocaine base and hydrochloride" in *Analytical Profiles of Drug Substances, Volume 14* (ibid, 1985) pp. 213.
20. F. J. Muhtadi, "Analytical Profile of Morphine" in *Analytical Profiles of Drug Substances, Volume 17* (ibid, 1988) pp. 267.
21. *The Merck Index, 11th Edition* (Merck & Co., Rahway, NJ, 1989) pp. 1948.
22. E. R. Oberholtzer, "Imipenem" in *Analytical Profiles of Drug Substances, Volume 17* (ibid, 1986) pp. 93.
23. I. A. Asher and G. Schwartman, "Ampotericin B" in *Analytical Profiles of Drug Substances, Volume 6* (ibid, 1977) pp. 11.
24. K. J. Pettersson, T. Nordgren and D. Westerlund, "Determination of phophonoformate (foscarnet) in biological fluids by ion-pair reversed-phase liquid chromatography", *J. Chromatogr.*, 488:447–455 (1989).
25. J. H. Burns, "Vinblastine Sulfate" in *Analytical Profiles of Drug Substances, Volume 1* (ibid, 1972) pp. 450.