convenience excellent or good. Of the 103 nurses, 80 opined that the PCA service saved them time, and several commented that a major advantage was that only one person, the clinical pharmacist, needed to be contacted for any problem. Seventy-one patients rated the PCA method highly, and most indicated that they would prefer a hospital with PCA services should they require surgery in the future.

Conclusion

Our comprehensive, pharmacy-based PCA service offers patients better control of pain with less sedation, allows pharmacists to demonstrate competence in nondistributive functions, increases the visibility of the pharmacy department to patients and the medical staff, and is a source of revenue. The service has been well accepted by patients, nurses, and physicians.

[a]Silverman HM, Bard MedSystems Division of C. R. Bard, Inc. Personal communication. 1986 Nov 11.

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Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers

HARRIE J. MARTENS, PIETER N. DE GOEDE, AND ARIE C. VAN LOENEN

Abstract: The sorption of chloroquine sulfate, diazepam, isosorbide dinitrate, lorazepam, midazolam, nitroglycerin, promethazine hydrochloride, thiopental sodium, and warfarin sodium to three types of containers was studied.

Appropriate amounts of the drugs were added to 500 mL of 0.9% sodium chloride injection in polyvinyl chloride (PVC) bags, glass bottles, and Clear-Flex bags composed of a laminate of polyethylene, nylon, and polypropylene. The containers were stored in the dark at room temperature for 24 hours. Samples were taken at various intervals and assayed for drug concentration by high-performance liquid chromatography.

There were no appreciable changes in pH after 24 hours, and all the admixtures remained clear and colorless. The potency of chloroquine sulfate, lorazepam, midazolam, promethazine hydrochloride, and thiopental sodium remained unchanged in glass, PVC, and Clear-Flex containers. Diazepam, isosorbide dinitrate, nitroglycerin, and warfarin sodium did not show any sorption to glass bottles and Clear-Flex bags. In PVC bags, however, up to 55% of diazepam, 23% of isosorbide dinitrate, 51% of nitroglycerin, and 24% of warfarin sodium was lost during the 24-hour study period.

Diazepam, isosorbide dinitrate, nitroglycerin, and warfarin sodium in 0.9% sodium chloride injection showed a loss of potency when stored in PVC containers for 24 hours at room temperature, but none of the drugs studied lost potency when stored in glass bottles and Clear-Flex bags.

Index terms: Additives; Anesthetics; Anticoagulants; Antihistamines; Antimalarial agents; Anxiolytics, sedatives and hypnotics; Chloroquine sulfate; Containers; Diazepam; Glass; Hydrogen ion concentration; Incompatibilities; Injections; Isosorbide dinitrate; Lorazepam; Midazolam; Nitroglycerin; Polyethylene; Polyvinyl chloride; Potency; Promethazine hydrochloride; Sodium chloride; Sorption; Stability; Storage; Thiopental sodium; Vasodilating agents; Warfarin sodium

Am J Hosp Pharm. 1990; 47:369–73

Certain drugs, including insulin, nitroglycerin, isosorbide dinitrate, chloroquine, clomethiazole, diazepam and other benzodiazepines, warfarin sodium, thiopental sodium, and some phenothiazines, show losses from aqueous solutions stored in infusion containers.[1–4] Such losses may result in reduced delivery of drugs to patients. Fortunately, drug loss from infusion solutions is likely to present a clinical hazard in only a few cases. Generally, these losses have been attributed to an interaction between the drug and the infusion container. Polyvinyl chloride (PVC) seems to be the main offender in this interaction.[2]

Documentation of the compatibility of drugs with infusion containers is limited. The main physicochemical determinants controlling sorp-

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tion of a drug appear to be the lipophilic properties of the drug, storage time and temperature, drug concentration, the extent of ionization (which is pH dependent), and the surface area-to-volume ratio of the container.[1]

With the recent introduction in Europe of a three-layer laminate bag (Clear-Flex) that is composed of polypropylene, nylon, and polyethylene and has low permeability to oxygen and water vapor,[5] it is important to know if drug sorption to this new material is less than with PVC. A similar bag is also available in the United States.[3] Polyethylene, the inner material, does not seem to show a substantial sorptive interaction with the drugs mentioned above.[3,4] The container material does not contain plasticizers and has an environmental advantage over PVC because it does not produce hydrochloric acid when it is burned.

The purpose of our study was to compare the sorptive profiles of chloroquine sulfate, diazepam, isosorbide dinitrate, lorazepam, midazolam hydrochloride, nitroglycerin, promethazine hydrochloride, thiopental sodium, and warfarin sodium in PVC, glass, and Clear-Flex containers.

Methods

Admixture Preparation. Drugs were added in appropriate amounts to 500 mL of 0.9% sodium chloride injection in PVC bags,[a] Clear-Flex bags,[b] and clear glass bottles[c] to obtain test solutions, which contained 12-hour dosages used in clinical practice. Chloroquine sulfate test solution was prepared by adding 5 mL of the contents of chloroquine sulfate 50-mg/mL ampuls[d] in a plastic disposable syringe to the contents of the containers; diazepam by adding 4 mL of 5-mg/mL ampuls,[e] isosorbide dinitrate by adding 50 mL of 1-mg/mL ampuls,[f] lorazepam by adding 5 mL of 4-mg/mL ampuls,[g] midazolam hydrochloride by adding 4 mL of 5-mg/mL ampuls,[h] nitroglycerin by adding 10 mL of 5-mg/mL ampuls,[i] promethazine hydrochloride by adding 2 mL of 25-mg/mL ampuls,[j] and warfarin sodium by adding 2.5 mL of 2-mg/mL ampuls.[k] Thiopental sodium test solution was prepared by reconstituting a 0.5-g vial[l] of drug with 20 mL of water for injection. Approximately 40 mL of this solution was added to the Clear-Flex containers.

Conditions and Sampling. Each type of solution was prepared in triplicate. The test solutions were stored at room temperature (21 °C) for 24 hours and were protected from light. To comply with standard sterility guidelines involving the time of expiration of intravenous admixtures, a 24-hour study period was chosen. The 24-hour period represents the maximum storage time of i.v. admixtures in our hospital. The test solutions were visually inspected for color and clarity immediately after mixing and at 1, 2, 4, 6, and 24 hours. At each interval, duplicate samples were taken with 1-mL plastic disposable syringes[m] and were assayed by high-performance liquid chromatography (HPLC) to determine drug concentrations. For nitroglycerin and isosorbide dinitrate, additional samples were taken at 15 and 30 minutes. Solution pH was measured with a Consort P914 pH meter[n] immediately after mixing and at 24 hours.

HPLC Analysis. Drug concentrations were measured by HPLC at 21 ± 1 °C. A model 45 solvent-delivery pump,[o] a U6K injector[o] with a fixed 10-μL or 50-μL loop, a model 440 dual-wavelength detector,[o] and a Shimadzu Chromatopac C-R3A integrator[p] were used. A 10-μL portion (for warfarin, 50 μL) of each sample was injected into the HPLC system. The use of a fixed loop obviated the need for internal standardization. Separations were achieved for chloroquine on a Lichrosorb 10 RP 8 stainless steel column[p] (4.6 mm × 25 cm) with a mobile phase of water–tetrahydrofuran–triethylamine (96:4:0.75) adjusted to a final pH of 2.3 with 2 M nitric acid (flow rate, 2 mL/min); for diazepam, lorazepam, and thiopental on a Lichrosorb 10 RP 8 column with a mobile phase of water–methanol–tetrahydrofuran (50:50:5) (3 mL/min); for isosorbide dinitrate and nitroglycerin on a Lichrosorb 10 RP 8 column with a mobile phase of water–methanol (50:50) (2 mL/min); for midazolam and promethazine on a μ-Bondapak C_{18} stainless steel column[o] (3.9 mm × 30 cm) with a mobile phase of acetonitrile–0.1 M dibasic potassium phosphate buffer (33:67) adjusted to a final pH of 4.4 with phosphoric acid (1.7 mL/min); and for warfarin sodium on a Novapak C_{18} Radial-Pak cartridge[o] (8 mm × 10 cm) with a mobile phase of 1.5% acetic acid–acetonitrile (69:31) adjusted to a final pH of 4.2 with 1 M sodium hydroxide (4.2 mL/min). Detection took place at a wavelength of 254 nm except for isosorbide dinitrate and nitroglycerin, which were detected at 214 nm.

All other chemicals and reagents used were of analytical grade.[q] Drug concentrations were determined by comparing peak heights with those of standard solutions prepared by diluting one fifth of the volume of the drug products[a–f] used in admixture preparation with 0.9% sodium chloride injection to a final volume of 100 mL.

Precision and retention time data for each drug are listed in Table 1.

Results and Discussion

Chloroquine sulfate, lorazepam, midazolam, promethazine hydrochloride, and thiopental sodium in 0.9% sodium chloride injection did not decrease in concentration when stored in glass, PVC, and Clear-Flex containers (Table 2). There were no appreciable changes in pH (Table 3), and all admixtures remained clear and colorless after 24 hours.

The concentration of diazepam declined rapidly

Table 1.
Retention Time and Precision Data for the High-Performance Liquid Chromatographic Method Used

Drug	Retention Time (min)	Linearity (μg/mL)	Correlation Coefficient	Coefficient of Variation (%)
Chloroquine sulfate	5.2	125–500	1.000	0.3 (n = 9)
Diazepam	10.0	20–40	0.9997	0.8 (n = 9)
Isosorbide dinitrate	3.8	25–100	1.000	2.0 (n = 6)
Lorazepam	8.0	20–40	0.9997	0.6 (n = 9)
Midazolam hydrochloride	5.1	10–40	1.000	2.5 (n = 6)
Nitroglycerin	5.8	25–100	1.000	2.0 (n = 6)
Promethazine hydrochloride	5.5	25–100	1.000	1.5 (n = 6)
Thiopental sodium	11.2	100–2000	0.9999	0.8 (n = 9)
Warfarin sodium	14.0	2.5–10	0.9995	3.6 (n = 9)

Table 2.
Sorption of Drug Admixtures in 0.9% Sodium Chloride Injection in Different Containers Stored at 21 °C in Darkness[a]

Drug and Container	Actual Initial Concentration (μg/mL)	% Remaining						
		15 min	30 min	1 hr	2 hr	4 hr	6 hr	24 hr
Chloroquine sulfate								
Glass bottle	482 ± 8.8	...	...	100.3 ± 0.4	99.9 ± 0.6	100.0 ± 0.5	99.8 ± 0.2	100.5 ± 0.6
PVC[b] bag	482 ± 6.1	...	...	100.1 ± 0.7	100.8 ± 0.8	99.8 ± 1.2	98.9 ± 0.8	98.4 ± 1.1
Clear-Flex bag[c]	497 ± 4.2	...	...	101.1 ± 0.5	100.2 ± 1.3	100.0 ± 0.9	99.2 ± 0.9	99.0 ± 1.4
Diazepam								
Glass bottle	38.6 ± 1.2	...	...	100.6 ± 0.3	99.7 ± 1.3	100.3 ± 1.6	99.8 ± 2.2	99.1 ± 2.8
PVC bag	37.3 ± 2.1	...	...	95.5 ± 1.3	85.1 ± 2.5	77.3 ± 3.6	66.9 ± 4.4	45.3 ± 2.5
Clear-Flex bag	39.1 ± 0.6	...	...	99.6 ± 1.5	100.4 ± 1.1	101.0 ± 1.2	99.5 ± 0.8	98.5 ± 0.7
Isosorbide dinitrate								
Glass bottle	95.3 ± 2.1	101.2 ± 1.8	100.0 ± 0.9	100.8 ± 0.7	99.7 ± 1.1	100.2 ± 1.5	99.6 ± 1.2	100.3 ± 1.4
PVC bag	93.0 ± 4.1	99.1 ± 2.1	96.8 ± 1.9	94.1 ± 1.7	90.8 ± 2.2	88.8 ± 2.8	84.7 ± 1.8	77.3 ± 2.6
Clear-Flex bag	98.8 ± 1.5	99.1 ± 1.3	99.5 ± 1.5	98.1 ± 1.5	97.9 ± 1.9	98.3 ± 0.9	101.2 ± 2.4	98.5 ± 2.1
Lorazepam								
Glass bottle	38.9 ± 2.2	...	...	101.3 ± 1.1	102.1 ± 2.1	100.2 ± 1.5	99.6 ± 0.4	99.2 ± 0.6
PVC bag	38.1 ± 3.0	...	...	99.1 ± 0.9	99.3 ± 0.8	97.8 ± 1.0	98.8 ± 1.1	97.4 ± 1.3
Clear-Flex bag	39.4 ± 0.8	...	...	100.1 ± 0.6	99.3 ± 1.1	98.5 ± 0.7	99.1 ± 0.9	98.6 ± 1.7
Midazolam								
Glass bottle	36.4 ± 2.2	...	...	101.3 ± 0.8	99.7 ± 0.6	100.5 ± 1.5	100.8 ± 1.2	102.1 ± 2.1
PVC bag	36.1 ± 4.2	...	...	99.1 ± 0.7	99.5 ± 1.3	99.8 ± 1.3	97.7 ± 1.8	98.3 ± 1.9
Clear-Flex bag	39.6 ± 1.1	...	...	100.7 ± 0.8	101.2 ± 1.2	100.1 ± 1.6	100.6 ± 1.9	102.0 ± 1.8
Nitroglycerin								
Glass bottle	102 ± 3.9	100.2 ± 0.5	100.5 ± 0.7	99.3 ± 1.1	99.1 ± 0.6	100.5 ± 1.5	98.8 ± 1.1	97.8 ± 1.3
PVC bag	101 ± 3.1	96.2 ± 0.9	91.0 ± 2.2	89.5 ± 2.7	86.5 ± 3.8	79.1 ± 4.1	67.8 ± 5.8	49.4 ± 6.2
Clear-Flex bag	106 ± 2.1	99.7 ± 1.2	100.3 ± 1.5	99.0 ± 1.5	98.5 ± 1.3	97.2 ± 1.9	95.1 ± 2.1	94.5 ± 2.6
Promethazine hydrochloride								
Glass bottle	95.2 ± 1.9	...	...	100.1 ± 0.5	99.8 ± 0.6	101.0 ± 1.5	100.8 ± 1.0	100.5 ± 0.4
PVC bag	90.4 ± 4.1	...	...	99.7 ± 0.6	100.2 ± 0.7	99.8 ± 1.2	98.6 ± 1.3	98.1 ± 1.7
Clear-Flex bag	96.3 ± 2.3	...	...	100.3 ± 0.9	100.6 ± 1.1	100.1 ± 0.8	99.9 ± 1.9	101.7 ± 2.0
Thiopental sodium								
Glass bottle	1803 ± 32	...	...	99.3 ± 1.4	99.9 ± 1.6	97.8 ± 1.5	97.8 ± 1.2	98.1 ± 1.8
PVC bag	1746 ± 44	...	...	100.4 ± 1.7	100.4 ± 1.9	99.6 ± 1.4	98.9 ± 1.8	97.8 ± 2.1
Clear-Flex bag	1817 ± 29	...	...	99.4 ± 1.5	100.1 ± 1.6	100.2 ± 1.9	99.2 ± 1.4	99.1 ± 1.2
Warfarin sodium								
Glass bottle	10.5 ± 0.4	...	...	101.3 ± 2.4	100.9 ± 2.6	102.0 ± 2.5	100.8 ± 3.2	100.1 ± 3.2
PVC bag	9.5 ± 0.7	...	...	96.8 ± 1.3	94.2 ± 1.8	89.1 ± 1.2	87.9 ± 1.1	76.5 ± 0.7
Clear-Flex bag	10.3 ± 0.5	...	...	100.4 ± 0.8	98.8 ± 1.1	98.2 ± 1.9	99.2 ± 1.0	97.2 ± 1.4

[a] Values expressed as mean ± S.D. for three determinations.
[b] PVC = polyvinyl chloride.
[c] Medital, Ede, The Netherlands, lot 86 K 17-4234.

Table 3.
pH Values for Drug Admixtures in 0.9% Sodium Chloride Injection in Different Containers Stored at 21 °C in Darkness[a]

Drug	Initial pH			pH after 24 hr		
	Glass Bottle	PVC[b] Bag	Clear-Flex[c] Bag	Glass Bottle	PVC Bag	Clear-Flex Bag
Chloroquine sulfate	6.9 ± 0.10	6.8 ± 0.06	6.8 ± 0.04	7.0 ± 0.05	6.8 ± 0.06	6.8 ± 0.04
Diazepam	6.8 ± 0.05	6.8 ± 0.03	6.6 ± 0.05	6.7 ± 0.07	6.8 ± 0.03	6.7 ± 0.05
Isosorbide dinitrate	6.8 ± 0.09	6.6 ± 0.04	6.6 ± 0.06	6.6 ± 0.08	6.8 ± 0.05	6.6 ± 0.02
Lorazepam	6.3 ± 0.04	6.5 ± 0.05	6.2 ± 0.07	6.5 ± 0.07	6.3 ± 0.04	6.3 ± 0.06
Midazolam	6.3 ± 0.05	5.9 ± 0.08	6.5 ± 0.03	6.5 ± 0.06	6.0 ± 0.07	6.6 ± 0.03
Nitroglycerin	6.6 ± 0.02	6.4 ± 0.03	6.4 ± 0.05	6.6 ± 0.02	6.4 ± 0.04	6.2 ± 0.09
Promethazine hydrochloride	6.3 ± 0.04	5.9 ± 0.08	6.5 ± 0.07	6.3 ± 0.03	5.7 ± 0.08	6.3 ± 0.10
Thiopental sodium	9.1 ± 0.02	9.1 ± 0.05	9.1 ± 0.08	9.0 ± 0.08	9.1 ± 0.04	9.2 ± 0.09
Warfarin sodium	6.0 ± 0.02	6.2 ± 0.07	6.1 ± 0.06	6.1 ± 0.05	6.0 ± 0.08	6.0 ± 0.05

[a] Values expressed as mean ± S.D. for three determinations.
[b] PVC = polyvinyl chloride.
[c] Medital, Ede, The Netherlands, lot 86 K 17-4234.

in the PVC container (Table 2), decreasing 15% within two hours and 55% at 24 hours. The sorption of diazepam to PVC has been reported previously.[1,3,4,6,7] Cloyd et al.[6] reported a reduction in diazepam concentration of about 55% in 24 hours. No sorption of diazepam was observed to occur in Clear-Flex or glass containers over at least 24 hours.

Isosorbide dinitrate showed a 23% decrease in concentration after 24 hours of storage in the PVC containers (Table 2). Most of the decrease occurred during the first six hours (15% loss). Similar results were found by Lee and Fenton-May,[8] who reported that isosorbide dinitrate is stable in PVC for only two hours and that after 24 hours the loss is about 30%. We observed no marked decrease of isosorbide dinitrate in Clear-Flex or glass containers.

Nitroglycerin retained potency for at least 24 hours in Clear-Flex and glass containers. As expected, nitroglycerin was incompatible with PVC.[4,9,10] A 10% decrease was seen after 1 hour, and after 24 hours only 49% of the initial concentration was measured (Table 2). This is in agreement with the results of Baaske et al.,[9] who reported a 42% decrease in nitroglycerin concentration after 24 hours of storage in PVC containers at room temperature.

Warfarin sodium did not show any sorption in Clear-Flex and glass containers. However, warfarin sodium concentration decreased 24% after 24 hours of storage in PVC containers (Table 2). These results conflict with those of Kowaluk et al.,[1] who found that warfarin sodium (22 μg/mL, pH 6.7) was stable after 24 hours and that only 15% was lost after one week.

Unlike Kowaluk et al.,[1] we did not observe any decrease in thiopental sodium concentration in PVC containers. This can be explained by differences in the methods used. In our study the concentration of the test solution was 2000 μg/mL to represent a therapeutic dosage (Table 2), while Kowaluk et al. used a concentration of 7 μg/mL, which allowed direct spectrophotometric assay without further dilution. This resulted in a negligible loss of thiopental sodium at pH 9.1, as in our study, but a 15% loss at pH 6.0.[1] The differences can be explained by the different pH values. For an acidic drug like thiopental sodium, sorption is faster at low pH because a greater fraction of the drug is nonionized. It seems that the concentration-dependent sorptive process for thiopental sodium suggested by Kowaluk et al. is dependent on solution pH rather than on a saturable sorptive process.

The loss of chloroquine hydrochloride due to sorption reported by Geary et al.,[11] 30–40% of a 32-μg/mL solution in glass test tubes, was not confirmed in our study. Whether this discrepancy is the result of a difference in chloroquine formulation or glass quality can be resolved only by further investigation.

Conclusion

Diazepam, isosorbide dinitrate, nitroglycerin, and warfarin sodium in 0.9% sodium chloride injection showed a loss of potency when stored in PVC containers for 24 hours at room temperature, but none of the drugs studied lost potency when stored in glass bottles and Clear-Flex bags.

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[a] Viaflex, Baxter, Utrecht, The Netherlands, lot 87A 07 A4.
[b] Medital, Ede, The Netherlands, lot 86102205; also available as Soluflex; not available in the United States.
[c] Lansberg, Uden, The Netherlands, lot 86 K 17-4234.
[d] Nivaquine 100 mg/2 mL, Rhone-Poulenc, Amstelveen, The Netherlands, lot 82J13-101.
[e] Diazepam injection 10 mg/2 mL, Centrachemie, Ettenleur, The Netherlands, lot 85L28A.
[f] Cedocard 10 mg/10 mL, Cedona, Haarlem, The Netherlands, lot 86L13.
[g] Temesta 4 mg/mL, Wyeth, Hoofddorp, The Netherlands, lot 87B18-7013.
[h] Dormicum 5 mg/mL, Hoffmann-LaRoche, Mijdrecht, The Netherlands, lot bo28-86J22.
[i] Nitroglycerin-Pohl 50 mg/10 mL, Tramedico, Weesp, The Netherlands, lot 85L19.

[j] Promethazine hydrochloride injection 50 mg/2 mL, own pharmacy production, lot 86L15-61.
[k] Warfarin sodium injection 2 mg/mL, own pharmacy production, lot 86H15-63.
[l] Nesdonal, Specia, Amstelveen, The Netherlands, lot 86F24-6541-1.
[m] Monoject, s'Hertogenbosch, The Netherlands, lot 86E15.
[n] Salm en Kipp, Breukelen, The Netherlands.
[o] Waters Associates, Etten-Leur, The Netherlands.
[p] Chrompack-Packard, Middelburg, The Netherlands.
[q] Merck, Amsterdam, The Netherlands.

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Recovery of phenytoin suspension after in vitro administration through percutaneous endoscopic gastrostomy Pezzer catheters

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Abstract: Various methods of administering phenytoin suspension through a percutaneous endoscopic gastrostomy (PEG) Pezzer catheter were evaluated in vitro to determine which method resulted in the most complete recovery of phenytoin.

To determine the effect of temperature on phenytoin recovery, 12 mL of phenytoin suspension (Dilantin-125, 125 mg/5 mL) was administered through three separate 35.5-cm 20 French latex PEG Pezzer catheters under each of three temperature conditions (suspension 11.8 °C and catheter 22 °C, suspension and catheter 22 °C, and suspension 22 °C and catheter 37 °C). To determine the effect of the administration method, 12-mL aliquots of phenytoin suspension were injected into the catheter by seven methods that varied with respect to catheter temperature, dilution of suspension, and irrigation of catheter. Each method was tested in triplicate, and samples were assayed by high-performance liquid chromatography.

Varying the temperature of the catheter or suspension had little effect on the recovery of phenytoin. There was no appreciable loss of phenytoin when the suspension was undiluted, regardless of whether the catheter was irrigated. The greatest losses were seen when the suspension was diluted before administration. Irrigation also caused a decrease in recovery, but to a lesser extent than dilution.

Until the effects of administering multiple doses of phenytoin through PEG Pezzer catheters are investigated, phenytoin suspension should not be diluted before administration because of decreased recovery and increased administration time.

Index terms: Adsorption; Anticonvulsants; Catheters; Dilutions; Drug administration; Drug administration routes; Incompatibilities; Irrigation; Latex; Phenytoin; Stability; Suspensions; Temperature
Am J Hosp Pharm. 1990; 47:373–7

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The assistance of Elisa T. Lee, Ph.D., with statistical analysis and of Robert A. Magarian, Ph.D., and the Section of Medicinal Chemistry and Pharmacodynamics in allowing the use of their instrumentation for HPLC analysis is acknowledged.

Presented in part at the 22nd Annual ASHP Midyear Clinical Meeting, Atlanta, GA, December 10, 1987.