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Determination of Clindamycin 2-Palmitate in Clinical Human Serum Samples

T. F. BRODASKY ˣ and F. F. SUN

Abstract □ Clindamycin 2-palmitate, used in pediatric formulations, is readily hydrolyzed to clindamycin. During clinical investigations of this antibiotic, it was necessary to determine if unhydrolyzed clindamycin palmitate was present in the serum of clinical subjects. Chemical and enzymatic hydrolyses were unsuitable and instrumental techniques were ultimately developed. Two methods are described, one based on a combination of GLC and single-ion focused mass spectroscopy and a second using TLC and GLC. Examination of human serum from subjects receiving 300–600 mg clindamycin base equivalents of clindamycin palmitate hydrochloride revealed no statistically significant quantities of unhydrolyzed clindamycin palmitate.

Keyphrases □ Clindamycin 2-palmitate—determination in human serum using GLC and GLC–mass spectroscopy □ GLC—determination, clindamycin 2-palmitate in human serum □ GLC–mass spectroscopy—determination, clindamycin 2-palmitate in human serum

Clindamycin palmitate hydrochloride[1] (II) is the derivative of clindamycin used in pediatric formulations. The presence of the palmitate group markedly improves the taste characteristics of the derivative compared to the parent compound. Although the ester is not biologically active, it is readily hydrolyzed *in vivo* to clindamycin (I). During clinical studies, the question arose as to the presence of unhydrolyzed clindamycin 2-palmitate in human serum. Initially, attempts were made to hydrolyze the palmitate using specific esterases; although this approach was successful in urine samples, it failed in serum. Chemical hydrolysis in serum was unsuitable since the reaction, in addition to hydrolyzing clindamycin 2-palmitate, destroyed other biologically active metabolites of clindamycin (1). In some cases, this led to less biological activity after hydrolysis than was observed before.

At this point, studies were initiated which ultimately led to instrumental methods of detecting clindamycin 2-palmitate. Although the techniques do not require hydrolysis of the palmitate ester, it is necessary to prepare trimethylsilyl ether derivatives to impart volatility. Two independent studies will be described, one based on a GLC–mass spectroscopy technique and a subsequent method based on GLC only. Because of the need to extract the ester from serum samples prior to derivatization, poorer quantitation was achieved than had been expected. It was possible, however, to demonstrate the absence of unhydrolyzed clindamycin palmitate in clinical blood samples.

EXPERIMENTAL

GLC–Mass Spectroscopy Method—*Clindamycin 2-Palmitate Trimethylsilyl Ether (IV)*—A stock solution of II containing 10 μg/ml in analytical reagent grade pyridine (dried over sodium hydroxide pellets) was prepared. Then 100 μl of the II stock solution and 900 μl of the trimethylsilylation reagent[2] (V) [trimethylsilylimidazole–bis(trimethylsilyl)acetamide–trimethylchlorosilane (3:3:2)] were mixed in a dry, evacuated, 1-ml tube[3] and heated on a hot plate for 5 min at 75°. These solutions were used for initial GLC and GLC–mass spectroscopy studies. Solutions for structural correlation work were prepared in a similar manner from 20 mg of solid II and 1 ml of V.

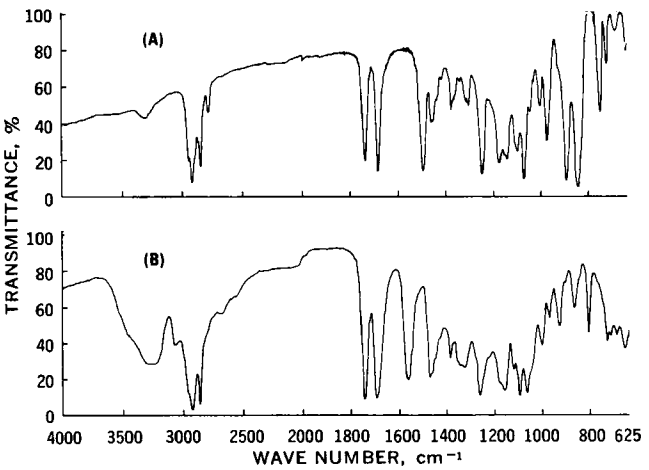


Figure 1—*Total reflectance IR spectra of II (B) and IV (A).*

[1] Cleocin Pediatric is The Upjohn Co. trademark for a product containing clindamycin palmitate hydrochloride (clindamycin 2-palmitate hydrochloride).

[2] Pierce Chemical Co.

[3] Reactivial, Supelco Co.

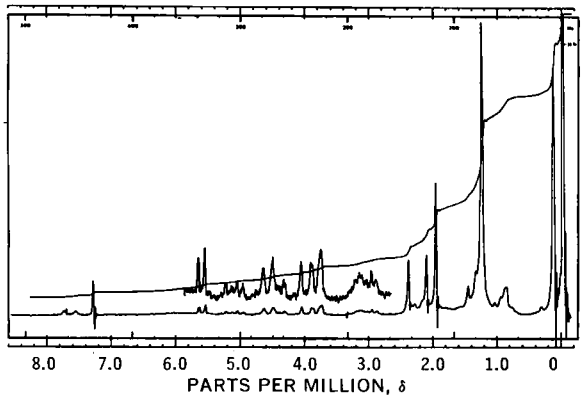


Figure 2—*NMR spectrum of IV (isolated solid).*

The solutions were stored at −10° when not in use. Under these conditions, IV was stable for several weeks.

Isolation and Characterization of IV—About 500 mg of II was treated with 3 ml of V as already described. After cooling, 50 ml of water was added to the reaction solution, which was then extracted with 75 ml of chloroform. The chloroform solution was evaporated to dryness under vacuum, and the resulting residue was characterized by IR, mass spectroscopy, NMR, and GLC.

Experimental Serum Samples—A solution containing 5 μg/ml II in 100 ml of pooled human serum[4] was prepared. After agitation, 4 volumes of acetone was added and the resulting precipitate was filtered and discarded. The filtrate was reduced to an aqueous solution under vacuum at 50°, and the pH was adjusted to 10 using potassium hydroxide. After extraction with hexane–methylene chloride (50:50), the mixture was centrifuged and the phases were separated. The solvent phase was dried with anhydrous sodium sulfate and, after filtering, was evaporated to dryness at 50° under vacuum. The entire residue was treated with 1 ml of V as previously described.

Clinical Serum Samples—Approximately 300 ml of blood was collected from each of four subjects prior to receiving 988 mg (600-mg base equivalents of clindamycin) of II (predrug blood) and another 300 ml each 1.5 hr after drug administration. The blood was allowed to stand at room temperature for 30 min, after which it was centrifuged for 30 min at 2000 rpm and the serum was collected. The predrug serums were pooled, but the postdrug serums were treated separately. By using the procedures described under *Experimental Serum Samples*, 100 ml of pooled predrug serum was prepared as a blank (no II added), 100 ml was spiked with 5 μg/ml of II, and another 100 ml was spiked with 1 μg/ml of II and derivatized as described. Each subject's postdrug serum (100–115 ml each) was treated as described for the predrug serum blank.

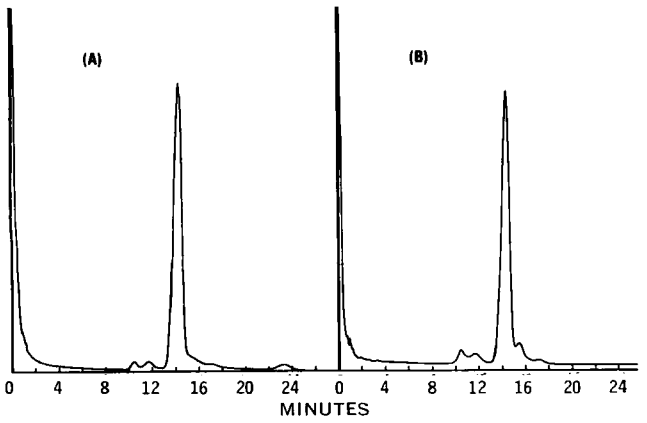
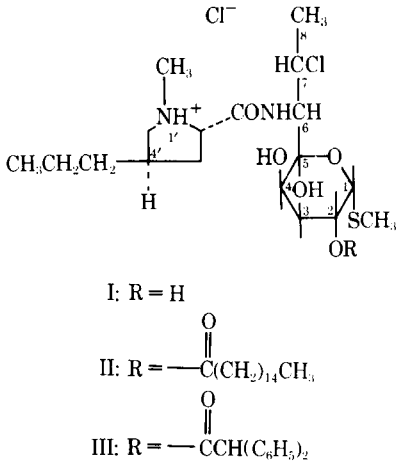


Figure 3—*Gas–liquid chromatogram of IV: (A) isolated solid, and (B) 20 mg/ml II and V reaction solution.*

[4] Grand Island Biological.



I: R = H

II: R = —C(CH₂)₁₄CH₃ (O)

III: R = —CCH(C₆H₅)₂ (O)

IR Spectroscopy—All IR spectra were recorded on a double-grating instrument[5] using double-beam total reflectance optics[6] and 50 × 2 mm KRS-5 plates.

NMR Spectroscopy—NMR spectra were recorded on a 60-MHz instrument[7] in deuterochloroform using tetramethylsilane as a reference. A sweep time of 250 sec and a sweep width of 500 Hz at an amplitude of 10 were used.

GLC—The gas-liquid chromatograms were recorded on a high efficiency, biomedical unit[8] using a 1.21-m (4-ft) × 0.63-cm (0.25-in.) glass column packed with a 3.8% UCW 98 on Diatoport S, 80–100 mesh. The column was operated in the isothermal mode at 300° and was monitored with a flame detector.

GLC–Mass Spectroscopy—The GLC-mass spectroscopy spectra were recorded[9] using a GLC column as already described. The column was limited to operation at 280° with the separator at 290°. The instrument was operated at 70 ev, and the source and detector slits were opened to three times normal. The detector was focused at a constant mass of *m/e* 126.4, and all other conditions were as described in the instrument manual specifications.

GLC Method—*Serum Extraction*—Five milliliters of serum in a 15-ml centrifuge tube was adjusted to pH 8 using 0.2 *M* KOH. After adding 0.25 ml of pH 8, 0.1 *M* tromethamine buffer, and 5 ml benzene, the tube was agitated for 15–30 min and then centrifuged for 10 min at 2000 rpm. The benzene layer was transferred to a 45-ml centrifuge tube, and the extraction of the serum was repeated twice more. The extracts were combined and evaporated to dryness under nitrogen.

TLC—A 20 × 20-cm silica gel plate was sectioned into five 4 × 20-cm strips. Serum extracts were streaked 0.5 cm from one end. The extraction tube was washed twice with 0.2-ml aliquots of chloroform, and the combined washes were also applied to the plate. Four strips were used for serum samples and the fifth for the II standard. The plates were irrigated in either of two mobile phases: *(a)* chloroform–ethyl acetate (3:1), and *(b)* hexane–ether–methyl ethyl ketone–methanol–ammonium hydroxide (70:15:15:3:0.25).

The best resolution was obtained by two unidimensional irrigations in the same system. After development, the strip containing the reference sample (II) was sprayed with permanganate–periodate reagent. The silica gel in the sample strips in the region of the R_f of the II standard was removed, and the ester was eluted into centrifuge tubes with five 5-ml portions of chloroform. The solvent was evaporated to dryness, and the vials were rinsed with a small amount of chloroform. The solvent was evaporated to dryness, and the vials were rinsed with a small amount of chloroform which was then transferred to a second centrifuge tube and evaporated to dryness for derivatization.

Trimethylsilylation—Clindamycin 2-diphenylacetate hydrochloride (III) was used as an internal standard for GLC analysis. One-half microgram was added to sample and standard extracts and unextracted standards with 0.1 ml of V, after which each

[5] Perkin-Elmer model 257.
[6] Wilks.
[7] Varian model T-60.
[8] Hewlett-Packard model 402.
[9] On an LKB 9000 GLC–mass spectroscopy unit.

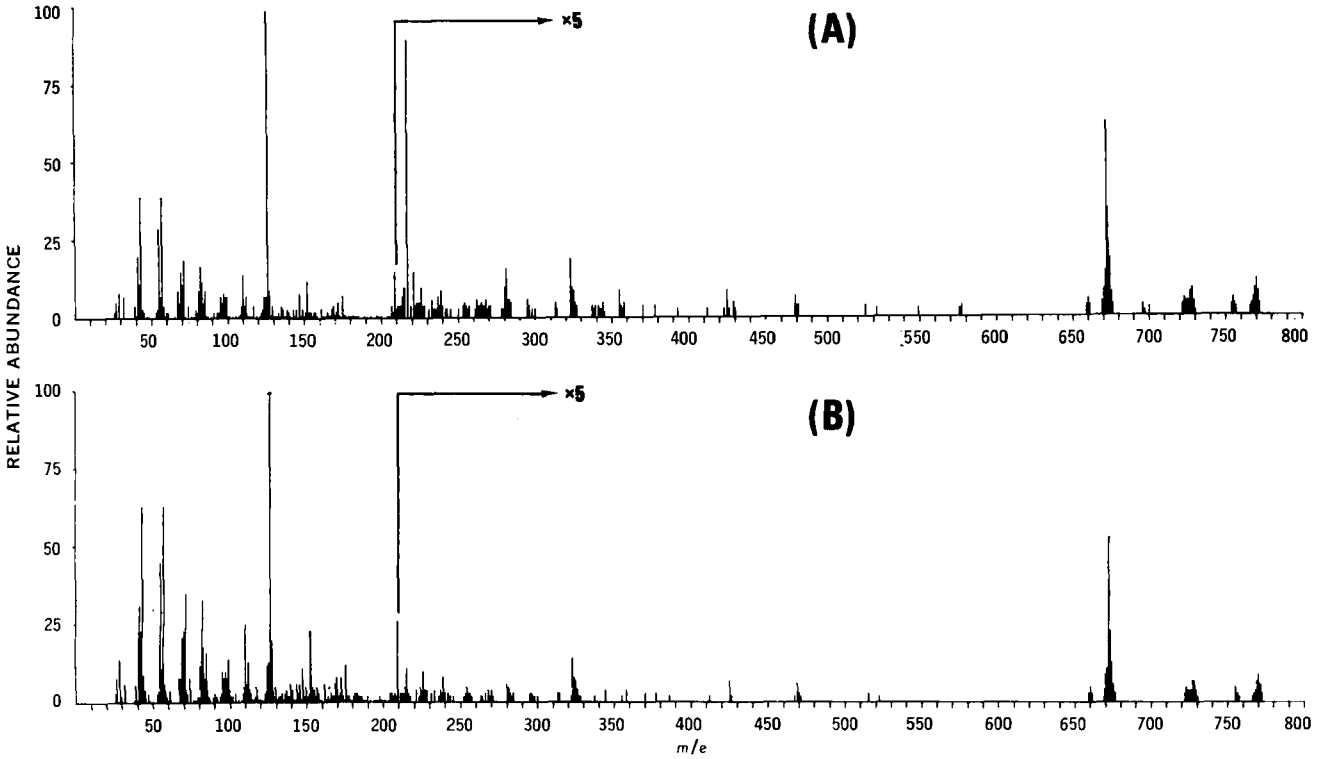


Figure 4—*Mass spectra of IV (using GLC–mass spectroscopic technique): (A) isolated solid, and (B) 20 mg/ml II and V reaction solution.*

tube was stoppered and shaken at room temperature for 20 min. The derivatives were extracted by adding 2 ml of cyclohexane and 1 ml of water to the tubes and shaking for 15 min or until no cloudiness was present in either phase. After separation, the aqueous layer was extracted with an additional 2 ml of cyclohexane, which was combined with the first extract and evaporated to dryness. The residues were dissolved in 2 ml of chloroform for analysis.

GLC Analysis—The analysis of IV was carried out on a GLC unit[8] using a 0.61-m (2-ft) × 0.63-cm (0.25-in.) o.d. glass column packed with a mixture of 1.5% (w/w) lexan and 1.5% (w/w) polysulfone on 80–100-mesh Gas Chrom Q. The column, operated isothermally at 295°, was monitored with a flame-ionization detector. Flow rates and other temperatures were consistent with manufacturer's manual specifications. The standard of IV was characterized[9] using the same column (temperature 290°). The mass spectrometer was operated as previously described.

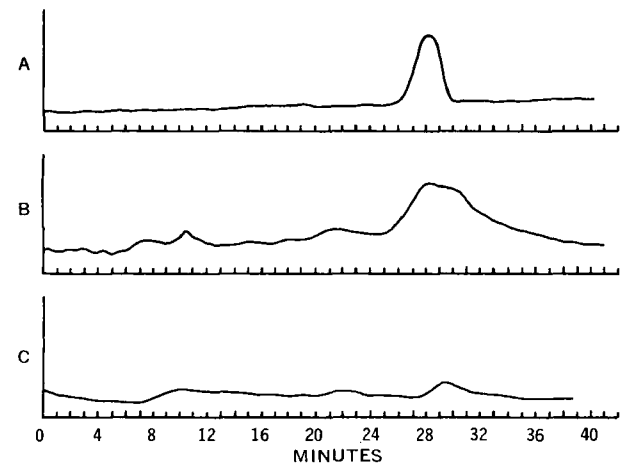


Figure 5—*Single-ion focused GLC–mass spectroscopy spectra of: (A) 1 μl, 1 mg/ml IV reaction solution (amplification ×1); (B) 2 μl, trimethylsilyl ether derivatized extract of 5 mg/ml II in serum (amplification ×10); and (C) 2 μl, trimethylsilyl ether derivatized extract of 1 mg/ml II in serum (amplification ×10).*

RESULTS AND DISCUSSION

GLC–Mass Spectroscopy Method—The basis of the GLC–mass

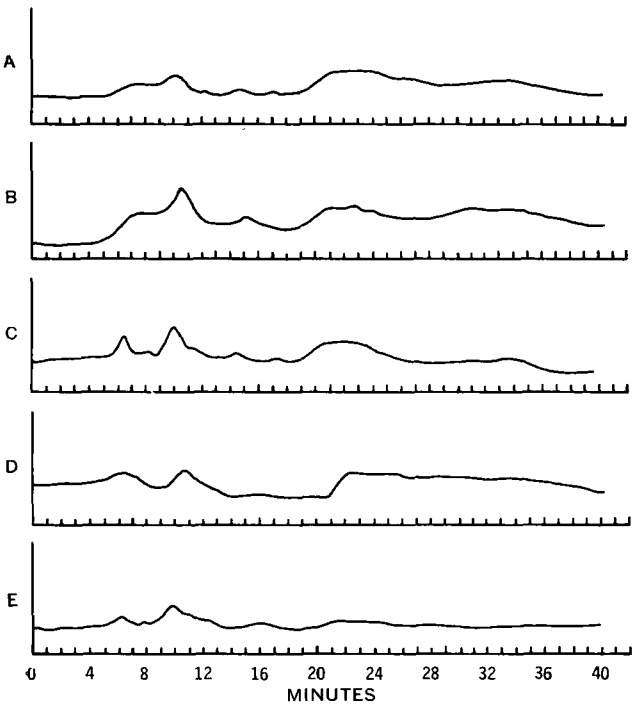


Figure 6—*Single-ion focused GLC–mass spectroscopy spectra of: (A–D) 2 μl, Subjects 1–4, derivatized serum extracts (amplification ×10); and (E) 2 μl, serum blank (amplification ×10).*

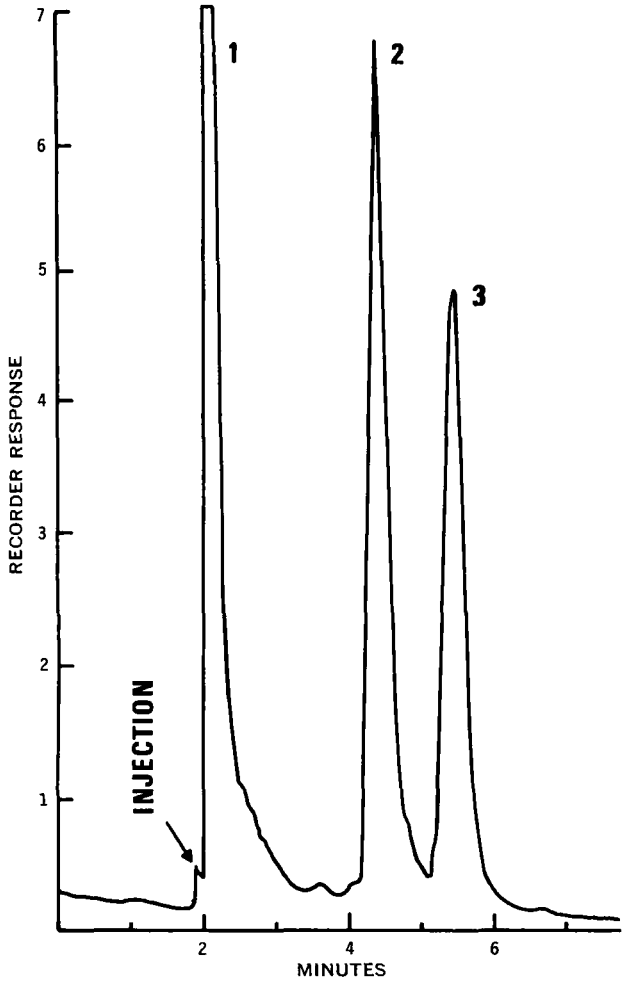
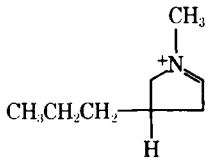


Figure 7—*Gas–liquid chromatogram of serum extract: (1) solvent, (2) IV, and (3) III silyl ether.*

spectroscopy method for the detection and quantitation of clindamycin palmitate is the observation of a peak (*m/e* 126) at a GLC retention time of 27–29 min in trimethylsilylated human serum extracts. In this single-ion monitoring technique (2), *m/e* 126 was chosen because it is the base peak of all clindamycin derivatives and results from a fragmentation reaction yielding the ion:



which carries 99% of the charge of the reaction. The inherently small yields of intact ester obtained from spiked serum samples and the nature of serum lyophilates and extracts precluded any direct characterization of IV in the samples except by comparison of GLC retention times and generation of the *m/e* 126 peak. To test the derivatization procedures and establish the nature of the derivatives, IV was prepared, isolated, and characterized by several methods. The internal reflectance IR spectra of clindamycin palmitate hydrochloride and its trimethylsilyl ether are shown in Fig. 1. The spectrum of the silyl ether is consistent with spectra of other similar derivatives prepared in this laboratory. Of particular significance is the lack of OH absorption and the presence of strong bands at 1250, 895, and 840 cm^{-1} [associated with O—$Si(CH_3)_3$ vibrations]. The bathochromic shift of the amide II band in clindamycin palmitate (1560 cm^{-1}) to 1500 cm^{-1} in IV is in keeping with a change in the ionic character of the compounds, clindamycin palmitate being the hydrochloride salt and IV a free base.

The NMR spectrum of IV is shown in Fig. 2. The spectrum is in agreement with the basic structure of clindamycin palmitate, the anomeric proton showing a doublet at 5.6 ppm and the NCH_3 and SCH_3 groups giving rise to singlets at 2.4 and 2.1 ppm, respectively.

The upfield shift of NCH_3 (normally at 3.0 ppm in clindamycin hydrochloride) agrees with the nonionic character of 1′-nitrogen in the free base. The intense peak at 1.24 ppm accounts for the 28 CH_2 protons in the palmitate ester group and two CH_2 protons in the 4′-propyl group (I). Using the integral for the 30 protons described, the peak at 0.15 ppm [—$Si(CH_3)_3$] integrates to 18 protons or two trimethylsilyl groups.

The gas–liquid chromatograms of isolated IV and a 20-mg/ml standard reaction solution of II and V are shown in Fig. 3. The retention times (14.5 min) are identical, thus indicating that the compound emerging from the column at this time is IV. The 20-mg/ml solution is typical of standard solutions used to establish retention times in this GLC–mass spectroscopy unit.

The mass spectra of both isolated IV and the 20-mg/ml standard solutions are shown in Fig. 4. The spectra were recorded after passage of the compound through the GLC column under the conditions described under *Experimental.* The retention time for both compounds is about 29 min. The molecular ion mass of 770 represents the disilyl ether of clindamycin palmitate minus *m/e* 36, which results from loss of hydrogen chloride through dehydrohalogenation of the 7,8- or 6,7-positions (see I). This reac-

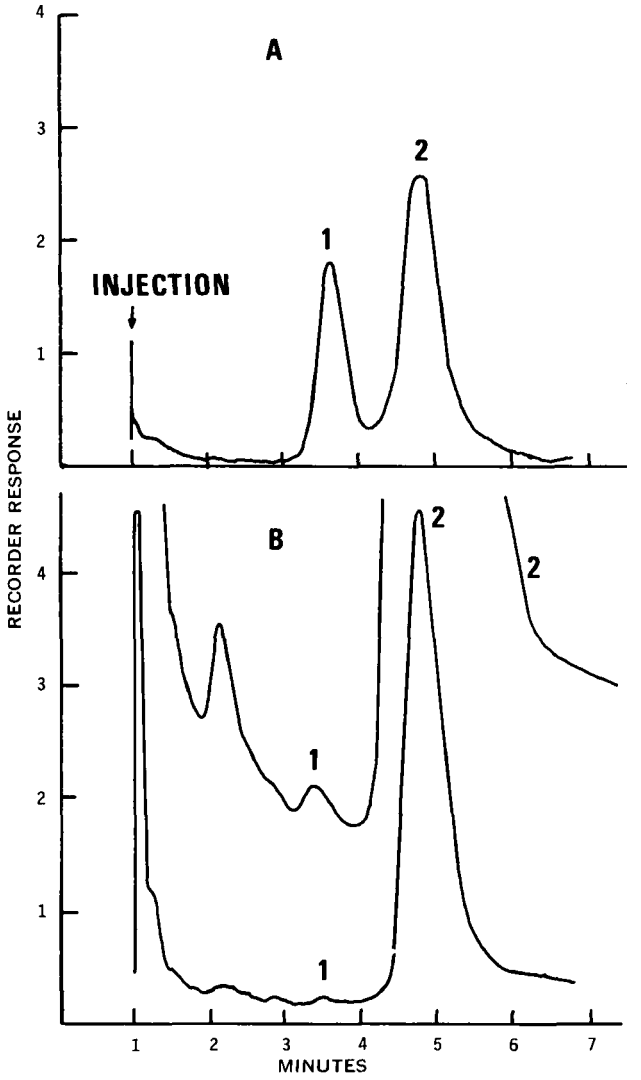


Figure 8—*Single-ion focused GLC–mass spectroscopy spectra of: (A) standard: 1, IV; 2, III silyl ether (amplification ×10); and (B) subject serum extract: 1, IV; 2, III silyl ether (upper amplification ×100, lower amplification ×10).*

Table I—Serum Concentrations of Free Clindamycin (Bioassay) and Clindamycin 2-Palmitate (GLC Assay) in Human Subjects following a Single Oral Dose of 300 mg Drug

Subject	Sampling Time, min	Clindamycin Bioactivity, μg/ml[a]	Estimate of Intact Clindamycin 2-Palmitate, μg/ml	Standard Deviation	95% Confidence Limits	
1	15	—[b]	0.1	0.3	−0.6	0.8
	30	1.99	0.2	0.3	−0.5	0.8
	45	—[b]	0.1	0.3	−0.6	0.8
	60	3.18	0.1	0.3	−0.6	0.8
2	15	—[b]	—[c]	—	—	—
	30	2.24	—[c]	—	—	—
	45	—[b]	—[c]	—	—	—
	60	2.29	—[c]	—	—	—
3	15	—[b]	0.2	0.3	−0.5	0.8
	30	1.32	—[c]	—	—	—
	45	—[b]	—[c]	—	—	—
	60	2.08	—[c]	—	—	—
4	15	—[b]	0.1	0.3	−0.7	0.7
	30	0.94	0.1	0.3	−0.6	0.7
	45	—[b]	0.1	0.3	−0.7	0.8
	60	1.57	—[c]	—	—	—
5	15	—[b]	0.1	0.3	−0.6	0.8
	30	1.29	—[c]	—	—	—
	45	—[b]	—[c]	—	—	—
	60	2.26	—[c]	—	—	—
6	15	—[b]	—[c]	—	—	—
	30	0.90	0.1	0.3	−0.6	0.8
	45	—[b]	—[c]	—	—	—
	60	1.17	—[c]	—	—	—
7	15	—[b]	0.2	0.2	−0.3	0.7
	30	1.71	0.4	0.3	−0.3	1.0
	45	—[b]	0.5	0.3	−0.2	1.2
	60	2.83	0.3	0.3	−0.4	0.9
8	15	—[b]	—[c]	—	—	—
	30	1.11	—[c]	—	—	—
	45	—[b]	0.1	0.3	−0.6	0.8
	60	1.52	0.1	0.3	−0.6	0.7

[a] By independent analysis. [b] No data available. [c] No measurable peak for clindamycin 2-palmitate observed in gas–liquid chromatogram.

tion occurs in all clindamycin compounds analyzed by mass spectroscopy. These data establish that the compound generated in the clindamycin palmitate silylation reactions is the disilyl ether.

The GLC–mass spectroscopy recordings for 1 μg of IV from a standard reaction solution and the derivatized 1- and 5-μg/ml clindamycin palmitate spiked predrug serums are shown in Fig. 5. The retention time for the 1-μg/ml spiked serum extract is slightly higher than that for other samples and reflects variation in the retention time associated with running samples on different days. Although actual quantity of II extracted from the spiked predrug serum was not determined, the mass chromatograms do indicate that it is possible to detect levels of 1 μg/ml (2 ng in 2-μl samples). The GLC–mass spectroscopy recordings for extracts of serum from clinical subjects are shown in Fig. 6. A predrug serum blank extract is included as a control.

Although there is considerable variation in the baselines of the serum extracts (most probably due to instrument variability and extracted blood solids), all subject serums showed minima in the region of 28–29 min. On the basis of this evidence, it was concluded that no more than 1 μg/ml clindamycin palmitate exists in the serum of these four subjects. The sensitivity of the method is based on the response of the 1-μg/ml spiked predrug serum extract. No statistically significant lower limit was placed on the sensitivity because of the lack of sufficient sampling. This was precluded by the inherent nature of the GLC–mass spectroscopy system to diminish in sensitivity on repetitive sampling of blood extracts due to source fouling. The presence of clindamycin in these serums had been established independently. Quantitation of samples of the same subject serums as used in this study indicated an average level of 4 μg/ml of clindamycin at the time the blood was drawn (1.5 hr).

GLC Method—This method, developed independently, is based on benzene extraction of serum samples, separation of the clindamycin palmitate from lipids by TLC, and subsequent quantitation of the trimethylsilyl ether derivatives by GLC. Experiments with various solvents and pH conditions revealed that benzene and pH 8 were optimum. Recovery of clindamycin palmitate from spiked serum samples, including the TLC step, varied between 23 and 49%, depending upon the subject serum used. Consistent recoveries were obtained for levels above 0.5 μg/ml of clindamycin palmitate, but recoveries varied considerably below this level. The clinical protocol used for subjects in this study differed from that used for the GLC–mass spectroscopy study in both dose and sampling times. Single oral doses of 494 mg II (300-mg base equivalents of clindamycin) with blood samplings at 0.25, 0.50, 0.75, and 1 hr were used for the GLC method, while 988-mg doses with blood samplings at 1.5 hr only were used for the GLC–mass spectroscopy technique. The latter was chosen since the peak serum levels of clindamycin after administration of clindamycin palmitate hydrochloride occur at 1–1.5 hr (3). The former conditions were chosen to cover shorter time periods in the event that clindamycin palmitate, if present, was being rapidly hydrolyzed.

Prior to analyzing all of the subject serums, IV (Fig. 7) was compared with one of the subject's serum by single-ion focused mass spectroscopy as previously described. The derivative had a fragment at m/e 126 and a retention time of 3.6 min and corresponded to a weak but observable peak in the serum sample (Fig. 8). The results of subsequent GLC analysis of all subjects' serums are given in Table I. Analysis of these results indicates that the concentration of clindamycin palmitate was below the level of assay sensitivity. This was determined by least-squares regression analysis of the standard curves which resulted in a lower limit of sensitivity, for which the 95% confidence limits did not include zero, of 0.66 μg IV/ml of serum. Therefore, after administration of a single oral dose of 494 mg II, the serum concentration of intact clindamycin palmitate in the blood could not be differentiated statistically from zero. Combined with the results

from the GLC–mass spectroscopy method, it is apparent that no significantly measurable quantities of clindamycin palmitate can be found in the serum of subjects receiving 494–988 mg of clindamycin palmitate hydrochloride 0.25–1.5 hr after administration.

Although GLC methods have been used extensively for the detection and quantitation of antibiotics and other pharmaceuticals, the single-ion focused mass spectroscopy method represents the application of a new mass spectroscopy technique to antibiotic research. With suitable sample extraction procedures, single-ion focusing can be a very specific and highly sensitive means of characterizing and quantitating antibiotics.

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[x] To whom inquiries should be directed.

Controlled Drug Release from Polymeric Devices I: Technique for Rapid *In Vitro* Release Studies

YIE W. CHIEN[x], HOWARD J. LAMBERT, and DONALD E. GRANT

Abstract □ A simple system was developed which allows the rapid and reproducible quantification of parameters influencing the release of drug by solid polymeric devices. The apparatus utilizes only 150 ml of elution medium and maintains "sink" conditions with water-miscible (nonaqueous) cosolvent combinations. Constant diffusion layer thickness is controlled by constant stirring and fixed temperature conditions. Factors influencing the rate of release of ethynodiol diacetate, a synthetic progestin, from solid silicone polymer vaginal devices were evaluated. The cumulative amount of drug released was proportional to the square root of time. The drug diffusivity was calculated and found in excellent agreement with previously reported data for similar compounds in silicone matrixes. The presence of a matrix-controlled process was confirmed by the independence of the steady-state diffusion rate on drug solubility in the eluant.

Keyphrases □ Drug release, controlled—method for measuring rapid *in vitro* release from polymer devices, ethynodiol diacetate from silicone polymers □ Transport, drug—rapid *in vitro* method for measuring steady-state drug release flux, ethynodiol diacetate from solid silicone polymer vaginal devices □ Permeation, drug—ethynodiol diacetate through solid silicone matrix, rapid *in vitro* method for measuring steady-state drug release flux □ Ethynodiol diacetate—release from solid silicone vaginal devices, effect of concentration and solubility of drug, rapid *in vitro* method for measuring steady-state drug release flux □ Contraceptives—rapid *in vitro* method for measuring ethynodiol diacetate release from solid silicone vaginal devices □ Vaginal devices—method for measuring drug release from polymer matrix

Recent interest has centered on the idea of replacing daily administration of a drug with delivery devices that release a constant effective dose to target tissues *via* a controlled-release mechanism (1–10). The high permeability of silicone polymer to steroids has been applied to the development of drug-filled and drug-impregnated silicone devices for long-acting hormonal contraception (11–24).

It is apparent from the literature that the development of a suitable measurement system is needed to understand drug release mechanisms in *in vivo* systems and also to correlate *in vitro* and *in vivo* drug release rate profiles accurately. An *in vitro* apparatus for studying the release of medroxyprogesterone acetate from a silicone device was designed (25). Because of the low aqueous solubility of medroxyprogesterone acetate, a large quantity (60 liters/day) of distilled water was used for dissolution to approximate a sink condition. The sensitivity of the diffusion cell was ignored (26–28). The drug release rate was determined weekly by assaying the residual drug content or measuring the thickness of the depletion zone in the devices. The same mechanical concepts were also applied in constructing a diffusion system for studying the release of progesterone from a polyethylene matrix (29).

One prime concern in making permeability measurements is the ability to determine the rate of drug release reliably in as short a time as possible (26–28). The development of such a technique and system should also make possible the direct measurement of drug release flux. With these considerations in mind, a relatively simple and easily constructed drug release system was designed, and a rapid, reproducible technique was developed. The ring-shaped polymeric device was mounted in a holder and rotated at constant speed in the elution medium so that constant hydrodynamics were maintained. This procedure allowed for a constant thickness of diffusion layer on the immediate surface of the device and a homogeneous drug concentration in the elution medium. Additionally, a polymer-compatible, drug-stable,