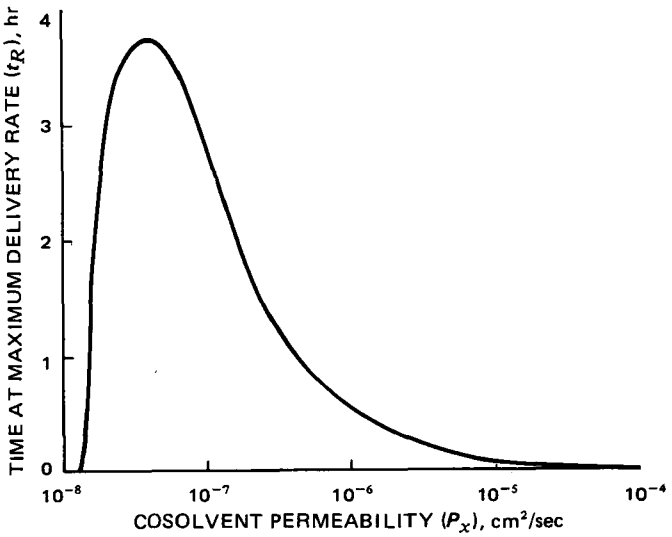


**Figure 6**—*Theoretical time at which a maximum in delivery rate occurs as calculated from Eq. 17 for progesterone diffusing from a polyethylene capsule ($X_i$ = 0.5 mole/liter).*

lease rate from a cosolvent system with linear solubility characteristics is described by Eq. 15 as a first approximation. The release rate is equal to the product of the limiting rate, initial drug concentration, and a function of time. This time function is dependent on capsule dimensions, on drug and cosolvent permeabilities and solubility characteristics, and on the initial cosolvent concentration. The time function is independent of initial drug loading. The time function is flexible and can be programmed into shapes exhibiting a maximum at a predetermined time or into a declining time pattern. In the limit at zero cosolvent concentration, the time function reduces to a simple first-order (exponential decay) release.

Different release rate profiles were experimentally produced which are in qualitative agreement with the theory. It follows from the theory that no maximum is expected in the cetyl alcohol system, which has a $P_x$ smaller than $P_{x0}$; for methyl and heptyl alcohols, a maximum is expected at 3.7 and 2.8 hr, respectively. The experimental permeability of heptyl alcohol is smaller than $P_{xm}$ and, therefore, the maximum is expected to lie between 0 and 3.7 hr, the latter time being the maximum time, for maximum rate, expected for the system geometry. Experimental $t_R$ times in excess of the theoretical maximum were not observed.

Since the theory as developed does not account for back-diffusion of cyclohexane, the influence of the cosolvent on membrane permeability characteristics, or for drug–cosolvent complexing (among other things), deviations can be expected where the membrane is affected by the presence of the cosolvent or where a strong cosolvent–drug interaction exists such that the complex diffuses as a separate species.

The release function predicts the attainment of a metastable, supersaturated state under certain tailored system conditions. A dosage form so designed could deliver a drug at rates exceeding those obtained from saturated solutions. During storage, the drug would remain in a stable solution state. When applied, a state of high thermodynamic activity can be produced *in situ* in a preprogrammed fashion.

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# Bioavailability of 17 Ampicillin Products

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**Abstract** □ The bioavailability of single lots of 250-mg ampicillin capsules, available from 17 distributors and/or manufacturers, was determined. Each product was evaluated in terms of the serum ampicillin levels achieved at 1, 2, 3, 4, 6, and 8 hr postadministration, the peak serum levels, the time of peak serum level, and the area under the serum level–time curve. There was no statistically significant difference ($p > 0.05$) between any of the 17 products tested.

**Keyphrases** □ Ampicillin—bioavailability of 17 products compared □ Bioavailability—ampicillin, 17 products compared □ Antibiotics—ampicillin, bioavailability of 17 products compared

It is well documented that while simple quantitative analysis of various drug dosage forms may indicate essentially identical drug content, the quantity of drug absorbed from the dosage form following oral administration may differ significantly from product to product (1–4). Ampicillin recently was categorized as a drug with "moderate risk potential" for bioavailability failures (5). Furthermore, the statement by

Table I—Ampicillin Capsules Employed in the Bioavailability Studies

| Product[a] | Expiration Date | FDA Certified Potency[b] |
|---|---|---|
| 1A,B,C | 2/77 | 259 |
| 2A | 12/74 | 248 |
| 3A | 1/75 | 253 |
| 4A | 1/75 | 260 |
| 5A | 1/75 | 260 |
| 6A | 11/74 | 256 |
| 2B | 5/75 | 260 |
| 3B | 5/76 | 249 |
| 4B | 6/77 | 259[c] |
| 5B | 5/77 | 264 |
| 6B | 7/74 | 246 |
| 2C | 6/77 | 249 |
| 3C | 2/76 | 255 |
| 4C | 6/76 | 252 |
| 5C | 10/75 | 254 |
| 6C | 9/77 | 259 |
| 7C | 7/76 | 274 |

[a] Products 1A, B, and C from Bristol Labs. (Polycillin), Lot A2116, manufactured by Bristol Labs.; Product 2A from Spencer-Mead, Lot 4746, manufactured by Biocraft Labs.; Product 3A from Paramount Surgical Supply Corp., Lot 2017-136, manufactured by Zenith Labs.; Product 4A from Vangard Labs., Lot 4774, manufactured by Biocraft Labs.; Product 5A from Wolins Pharmacal Corp., Lot 4774, manufactured by Biocraft Labs.; Product 6A from Columbia Medical Co., Lot 2017-126, manufactured by Zenith Labs.; Product 2B from Bocan Drug Co., Lot 201-3-B-102, manufactured by International Labs.; Product 3B from United Research Labs., Lot 2017-154, manufactured by Zenith Labs.; Product 4B from Wyeth Labs., Lot 1721636, manufactured by Wyeth Labs.; Product 5B from The Upjohn Co., Lot 199AW-D2, manufactured by Bristol Labs.; Product 6B from Squibb Pharmaceutical Co., Lot 2A622, manufactured by Squibb Pharmaceutical Co.; Product 2C from Smith Kline & French, Lot 32101, manufactured by Bristol Labs.; Product 3C from Beecham-Massengill, Lot Z7181RB, manufactured by Beecham-Massengill; Product 4C from Lederle Labs., Lot 334-101, manufactured by Beecham-Massengill; Product 5C from Ayerst Labs., Lot A6871PK, manufactured by Beecham-Massengill; Product 6C from Parke-Davis, Lot ML126, manufactured by Bristol Labs.; and Product 7C from Pfizer, Inc., Lot 24517, manufactured by Beecham-Massengill. [b] Expressed as milligrams of ampicillin per capsule. [c] Anhydrous ampicillin; all other products are ampicillin trihydrate.

the Drug Bioequivalence Panel of the Office of Technology Assessment (6) included ampicillin in the list of 24 drugs that exhibited differences in bioavailability between chemically equivalent products.

One study (7) compared three different 250-mg ampicillin products in a crossover experiment involving 12 human subjects. No statistically significant differences were noted in the bioavailability following oral administration. In contrast, a recent study (8) showed statistically significant differences in the bioavailability of the three 250-mg ampicillin products tested.

The present study was undertaken to provide bioavailability information on the currently marketed ampicillin products.

## EXPERIMENTAL

**Assay**—The experimental design and the reported lack of stability of ampicillin in stored biological fluids (9, 10) required an assay method suitable for the rapid analysis of numerous samples. A microbiological, turbidimetric assay employing *Staphylococcus aureus*[1] was developed to quantitate serum ampicillin levels precisely and rapidly (10).

Venous blood samples were obtained following the oral administration of 250-mg capsules to human volunteers. The blood samples were allowed to clot, and the serum was separated within 30 min after collection and stored for no longer than 4 days at −10° until assayed.

[1] BMH 331-036, Baptist Memorial Hospital, Memphis, Tenn.

Table II—Experimental Design for Ampicillin Bioavailability Study, Series C[a]

| | Week of Study | | | | | | |
|---|---|---|---|---|---|---|---|
| Subject | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 1 | 1 | 2 | 7 | 3 | 6 | 4 | 5 |
| 2 | 1 | 2 | 7 | 3 | 6 | 4 | 5 |
| 3 | 2 | 3 | 1 | 4 | 7 | 5 | 6 |
| 4 | 2 | 3 | 1 | 4 | 7 | 5 | 6 |
| 5 | 3 | 4 | 2 | 5 | 1 | 6 | 7 |
| 6 | 3 | 4 | 2 | 5 | 1 | 6 | 7 |
| 7 | 4 | 5 | 3 | 6 | 2 | 7 | 1 |
| 8 | 4 | 5 | 3 | 6 | 2 | 7 | 1 |
| 9 | 5 | 6 | 4 | 7 | 3 | 1 | 2 |
| 10 | 5 | 6 | 4 | 7 | 3 | 1 | 2 |
| 11 | 6 | 7 | 5 | 1 | 4 | 2 | 3 |
| 12 | 6 | 7 | 5 | 1 | 4 | 2 | 3 |
| 13 | 7 | 1 | 6 | 2 | 5 | 3 | 4 |
| 14 | 7 | 1 | 6 | 2 | 5 | 3 | 4 |

[a] Each number within the matrix corresponds to a specific product code number. In Series A and B, Subjects 1–12 were used and six products were evaluated.

**Clinical Study Protocol**—The 14 male volunteers[2] had an average age of 24 years (range 20–38 years), an average height of 175.3 cm (range 167.6–190.5 cm), and an average weight of 75.5 kg (range 63.6–90.9 kg). Each volunteer was screened regarding general health and known drug allergies. All subjects underwent a hematologic and blood chemistry analysis[3] to ensure inclusion of only those subjects in good health. Each subject provided his informed written consent.

The bioavailability study of the 17 ampicillin products (Table I) was divided into three separate segments: Series A and B (12 subjects, 6 weeks, six products) and Series C (14 subjects, 7 weeks, seven products). Each subject received each drug in a sequence designed to minimize the influence of any cumulative or residual effects of preceding doses (11) (Table II). Product 1 was included in each series as a reference to permit comparisons.

All subjects were instructed to adhere to a standard protocol and to abstain from taking any medication for 1 week prior to and during each study. On the day of the study, following an overnight fast, each subject had an indwelling catheter[4] inserted into a forearm vein and a 10-ml blood sample was taken. A single ampicillin capsule was then swallowed with 240 ml (8 oz.) of water. No food or liquid other than water was permitted for 4 hr following ingestion of the dose. Ten-milliliter blood samples were withdrawn at 1, 2, 3, 4, 6, and 8 hr postadministration.

## RESULTS AND DISCUSSION

Currently, antibiotic products must be certified for potency by the Food and Drug Administration (FDA), and each manufacturer was requested to provide the certification results (Table I).

There are almost 50 distributors of ampicillin products in the United States. However, FDA has approved the manufacture of ampicillin capsules by only the following eight companies: Beecham-Massengill Pharmaceutical, Biocraft Labs., Bristol Labs., International Labs., Linden Labs., E. R. Squibb & Sons, Wyeth Labs., and Zenith Labs. (9). This study encompassed all these manufacturers except Linden Labs.

To compare the relative bioavailability of 17 ampicillin products, four parameters describing the blood level curves were evaluated. These were: (*a*) serum concentrations achieved at 1, 2, 3, 4, 6, and 8 hr postadministration; (*b*) the peak serum concentration; (*c*) the time of peak concentration; and (*d*) the area under the serum concentration–time curve.

**Serum Concentrations**—The mean ampicillin serum levels observed are shown graphically in Figs. 1–3. Statistical analysis of these data revealed no significant differences ($p > 0.05$) between

[2] Recruited from the staff and student body of the University of Tennessee Center for the Health Sciences.
[3] SMA 12/60.
[4] Minicath PRN, Deseret Pharmaceutical Co., Sandy, Utah.

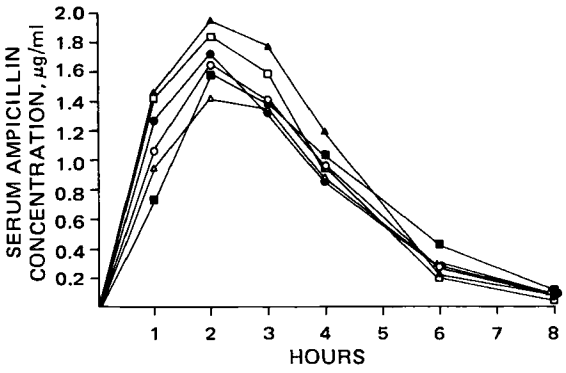


**Figure 1**—*Mean serum ampicillin levels for six products (Series A) administered to 12 subjects. Key: ●, Product 1A; ○, Product 2A; ■, Product 3A; □, Product 4A; ▲, Product 5A; and △, Product 6A. (See Table I for product code.)*

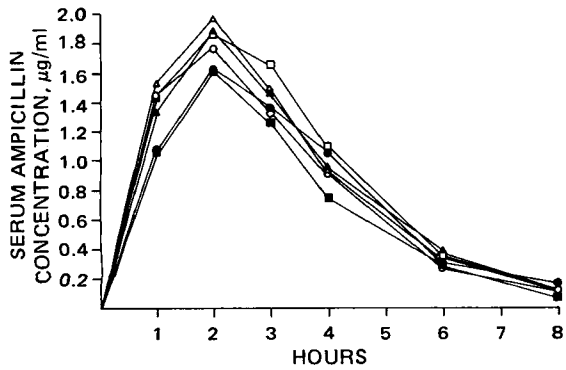


**Figure 2**—*Mean serum ampicillin levels for six products (Series B) administered to 12 subjects. Key: ●, Product 1B; ○, Product 2B; ■, Product 3B; □, Product 4B; ▲, Product 5B; and △, Product 6B. (See Table I for product code.)*

the products evaluated within each series in terms of the average serum levels at 1, 2, 3, 4, 6, and 8 hr postadministration.

**Peak Serum Concentration**—The magnitude of the peak serum level is a function of both the rate and extent of drug absorption. The average peak serum concentration for all tested products was 1.96 μg/ml (range 1.5–2.42 μg/ml). The analysis of variance for the peak serum level data showed no significant differences ($p > 0.05$) in peak serum level for any product tested.

**Time of Peak Serum Concentration**—This parameter is a function of the rate of drug absorption. The average time to achieve the peak serum concentration for all tested products was 2.14 hr (range 1.79–2.58 hr) after drug administration. A statistical analysis of the average time required to achieve the peak ampicillin serum levels for each product indicated no significant differences ($p > 0.05$).

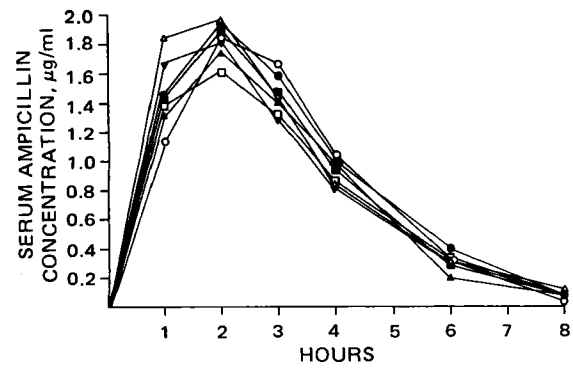


**Figure 3**—*Mean serum ampicillin levels for seven products (Series C) administered to 14 subjects. Key: ●, Product 1C; ○, Product 2C; ■, Product 3C; □, Product 4C; ▲, Product 5C; △, Product 6C; and ▼, Product 7C. (See Table I for product code.)*

**Table III—Data for Series A**

| Product[a] | Summary of Average *AUC*: Average *AUC*[b], (μg/ml) × hr | *CV*, % | Percent Relative to Product 1A |
|---|---|---|---|
| 5A | 7.64 (0.74) | 33.67 | 122.8 |
| 4A | 6.96 (0.63) | 31.52 | 111.9 |
| 3A | 6.32 (0.47) | 26.00 | 101.6 |
| 1A | 6.22 (0.54) | 30.01 | 100.0 |
| 2A | 6.17 (0.58) | 32.30 | 99.2 |
| 6A | 5.74 (0.45) | 27.44 | 92.3 |

Analysis of Variance for *AUC*

| Source of Variance | Sum of Squares | Degrees of Freedom | Mean Squares | *F* Ratio |
|---|---|---|---|---|
| Between subjects | | | | |
| Groups | 2.684 | 5 | 0.537 | 0.039 |
| Subjects within groups | 81.547 | 6 | 13.591 | |
| Within subjects | | | | |
| Weeks | 24.485 | 5 | 4.897 | 1.747 |
| Products | 27.899 | 5 | 5.580 | 1.991[c] |
| Product–week interaction | 72.166 | 20 | 3.608 | 1.287 |
| Error (within) | 84.065 | 30 | 2.802 | |

[a] See Table I for products. [b] Average of 12 subjects; standard error in parentheses. [c] Not significant ($p > 0.05$).

**Area under Serum Concentration-Time Curve (*AUC*)**—The *AUC* values summarized (Tables III–V) are indicative of the relative amounts of ampicillin absorbed from each test product. Tables I–III also show the *AUC*'s for each product relative to reference Product 1. The *AUC* values were determined with the aid of a planimeter.

Approximately 25% of the serum level curves were sufficiently elevated at the terminal 8-hr sampling time to require the application of Eq. 1 for the estimation of the total *AUC*:

$$(AUC)_{0-\infty} = (AUC)_{0-8\,hr} + \frac{(C_s)_{8\,hr}}{K} \qquad \text{(Eq. 1)}$$

where $(C_s)_{8\,hr}$ is the serum ampicillin level at the 8-hr sampling time, and $K$ is the elimination rate constant estimated from the terminal portion of a semilog plot of serum concentration *versus*

**Table IV—Data for Series B**

| Product[a] | Summary of Average *AUC*: Average *AUC*[b], (μg/ml) × hr | *CV*, % | Percent Relative to Product 1B |
|---|---|---|---|
| 4B | 7.31 (0.40) | 18.80 | 112.8 |
| 6B | 7.22 (0.61) | 29.23 | 111.4 |
| 5B | 6.88 (0.30) | 15.23 | 106.2 |
| 2B | 6.53 (0.41) | 21.99 | 100.8 |
| 1B | 6.48 (0.39) | 20.69 | 100.0 |
| 3B | 5.88 (0.45) | 26.40 | 90.7 |

Analysis of Variance for *AUC*

| Source of Variance | Sum of Squares | Degrees of Freedom | Mean Squares | *F* Ratio |
|---|---|---|---|---|
| Between subjects | | | | |
| Groups | 16.302 | 5 | 3.260 | 0.610 |
| Subjects within groups | 32.088 | 6 | 5.348 | |
| Within subjects | | | | |
| Weeks | 24.577 | 5 | 4.915 | 3.363 |
| Products | 17.090 | 5 | 3.418 | 2.339[c] |
| Product–week interaction | 33.870 | 20 | 1.694 | 1.159 |
| Error (within) | 43.842 | 30 | 1.461 | |

[a] See Table I for products. [b] Average of 12 subjects; standard error in parentheses. [c] Not significant ($p > 0.05$).

Table V—Data for Series C

Summary of Average *AUC*

| Product[a] | Average *AUC*[b], (μg/ml) × hr | *CV*, % | Percent Relative to Product 1C |
|---|---|---|---|
| 1C | 7.45 (0.56) | 28.05 | 100.0 |
| 6C | 7.38 (0.59) | 29.96 | 99.1 |
| 7C | 6.94 (0.51) | 27.32 | 93.2 |
| 2C | 6.83 (0.63) | 34.56 | 91.7 |
| 3C | 6.81 (0.69) | 38.03 | 91.4 |
| 5C | 6.45 (0.50) | 28.89 | 86.6 |
| 4C | 6.41 (0.54) | 31.36 | 86.0 |

Analysis of Variance for *AUC*

| Source of Variance | Sum of Squares | Degrees of Freedom | Mean Squares | *F* Ratio |
|---|---|---|---|---|
| Between subjects | | | | |
| Groups | 70.884 | 6 | 11.814 | 0.645 |
| Subjects within groups | 128.207 | 7 | 18.315 | |
| Within subjects | | | | |
| Weeks | 34.115 | 6 | 5.685 | 2.152 |
| Products | 13.828 | 6 | 2.305 | 0.872[c] |
| Product–week interaction | 80.304 | 30 | 2.677 | 1.013 |
| Error (within) | 110.972 | 42 | 2.642 | |

[a] See Table I for products. [b] Average of 14 subjects; standard error in parentheses. [c] Not significant ($p > 0.05$).

time. The mean half-life calculated from 64 individual serum level–time plots was 1.37 hr (*SE* 0.06). This value was in good agreement with previously reported values ranging from 1.0 to 1.3 hr (12, 13).

Tables III–V also summarize the statistical analysis of the *AUC* data. No statistically significant differences ($p > 0.05$) were observed for any tested product. Previous studies (14, 15) indicated that anhydrous ampicillin was approximately 8–17% better absorbed than the trihydrate form. Product 4B was the only anhydrous ampicillin evaluated. As indicated in Table IV, no statistically significant difference was observed between this product and the various trihydrate products tested.

The sensitivity of the experimental design was evaluated using the *F* ratio test described previously (7, 8). The differences in *AUC* between the product exhibiting the greatest mean *AUC* and the product exhibiting the lowest mean *AUC*, required for significance at the 0.05 level, were 18.3, 13.8, and 16.7% for Series A, B, and C, respectively. These differences indicated that the present study was more sensitive to differences in *AUC* than the work of Mayersohn and Endrenyi (7) but less sensitive than the study of MacLeod *et al.* (8). Application of the more stringent Newman–Keuls or Tukey test indicated that differences of 27.2, 20.5, and 25.6% for Series A, B, and C, respectively, would have been required for significance at the 0.05 level.

The absorption of ampicillin has been reported to exhibit considerable intrasubject and intersubject variability, with absorption following oral administration ranging from 20 to 70% of the dose (9). This study afforded an opportunity to investigate intrasubject variability upon repeated dosing, since each of 12 subjects took the reference Product 1 on three occasions, separated by at least 6 weeks. The *AUC*'s observed for these 12 subjects are shown in Table VI. Statistical analysis indicated no significant difference ($p > 0.05$) between the first, second, or third administration. However, several subjects, particularly Subjects 1 and 4, exhibited considerable variability in *AUC* between the three dose administrations. Subjects 8 and 9, who were identical twins, exhibited essentially the same average *AUC*'s.

Since several ampicillin products were manufactured by the same company but distributed by different companies, it was of interest to compare the bioavailability of presumably identical products administered to identical groups of subjects. Thus, Products 1C, 2C, and 6C were manufactured by the same company and were administered to the same subjects. Similarly, Products 1B and 5B, Products 3A and 6A, Products 3C, 4C, 5C, and 7C, and Products 2A, 4A, and 5A represent groups of products with identical manufacturers. A comparison of average *AUC* values among the individual products within each group indicates a maximum difference of only approximately 11%. This analysis further substantiates the methodology employed to assess the bioavailability of the ampicillin products, since those products for which little difference in absorption was anticipated exhibited very similar bioavailability.

Table VI—*AUC* for 12 Subjects Receiving Reference Product 1 on Three Separate Occasions[a]

| Subject | Series A | Series B | Series C | Mean (*SE*) | *CV*, % |
|---|---|---|---|---|---|
| 1 | 2.37 | 6.57 | 7.47 | 5.47 (1.57) | 49.76 |
| 2 | 6.63 | 9.98 | 9.99 | 8.87 (1.11) | 21.85 |
| 3 | 6.47 | 6.25 | 6.07 | 6.26 (0.11) | 3.20 |
| 4 | 4.17 | 6.52 | 9.79 | 6.82 (1.63) | 41.34 |
| 5 | 7.77 | 7.62 | 6.10 | 7.16 (0.53) | 12.90 |
| 6 | 7.80 | 6.82 | 11.20 | 8.61 (1.32) | 26.71 |
| 7 | 5.14 | 6.17 | 3.43 | 4.91 (0.80) | 28.17 |
| 8 | 6.26 | 5.75 | 8.05 | 6.68 (0.70) | 18.06 |
| 9 | 5.19 | 6.13 | 8.66 | 6.66 (1.04) | 26.95 |
| 10 | 7.62 | 6.17 | 5.19 | 6.32 (0.71) | 19.32 |
| 11 | 9.35 | 5.15 | 6.55 | 7.02 (1.23) | 30.48 |
| 12 | 5.83 | 4.63 | 5.86 | 5.44 (0.40) | 12.85 |
| Mean | 6.22 | 6.48 | 7.36 | | |
| *SE* | 0.54 | 0.39 | 0.65 | | |
| *CV*, % | 30.01 | 20.69 | 30.66 | | |

[a] *AUC*'s expressed as (micrograms per milliliter) (hour).

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# Solubilities of Testosterone Propionate and Related Esters in Organic Solvents

KENNETH C. JAMES [x], CHU TEK NG, and PETER R. NOYCE *

**Abstract** □ The solubility parameters of a range of saturated hydrocarbons were calculated from vapor pressures and heats of vaporization. Solubilities of testosterone propionate were determined in these solvents at 25° and yielded solute solubility parameters which varied from solvent to solvent. The solubility parameter of testosterone propionate was determined by several other methods, and support was found for the previously published figure of 9.5 $cal^{1/2}\ cm^{-3/2}$. The geometric mean coefficient ($l_{12}$) in saturated hydrocarbons was found to be a rectilinear function of the branching ratio ($r$). The mean $l_{12}$ of androstanolone and testosterone propionates was used to calculate the solubilities of other esters, giving good agreement with experimental results. IR data, presented as the sum of the shifts of the 3-keto and 17-ester carbonyl stretching frequencies in polar solvents, correlated rectilinearly with the geometric mean coefficients and the plot extrapolated to the $l_{12}$ value of $n$-hexane, calculated from the branching ratio plot. Attempts to predict solubilities of other esters in polar solvents using $l_{12}$ values achieved only limited success.

**Keyphrases** □ Testosterone propionate—related esters, solubility in various organic solvents □ Solubility—testosterone propionate and related esters in various organic solvents □ Hydrocarbons, saturated—solvents for testosterone propionate and related esters

The simplest model for a liquid solution is one where the solute and solvent have the same affinity for each other as they do for their own kind. Molecular distribution is then as random as can be permitted by molecular contact, and the solution is said to be ideal. Liquids that mix to form ideal solutions are mutually soluble in all proportions; but when the solute is a solid, solubility is limited because energy is necessary for liquefaction.

In real solutions, forces of intermolecular attraction are not uniform and like molecules tend to congregate together. When the solute and solvent have low polarities, thermal motion is sufficient to keep them randomly distributed, and solubility can be predicted (1) by:

$$-\ln X_2 = \frac{\Delta H^f}{R}\left[\frac{T_m - T}{T_m T}\right] + \frac{V_2\phi_1^2(\delta_1 - \delta_2)^2}{RT} \qquad \text{(Eq. 1)}$$

The first term on the right-hand side represents the natural logarithm of ideal solubility at temperature $T$; $\Delta H^f$ is the heat of fusion of the solute, and $T_m$ is the melting point. The second term represents the contribution of the heat of mixing, which is assessed in terms of the solubility parameters $\delta_1$ and $\delta_2$, the square roots of the cohesive energy densities of solvent and solute, respectively. The term $V_2$ is the molar volume of the solute, and $\phi_1$ is the volume fraction of the solvent.

Expansion of the $(\delta_1 - \delta_2)^2$ term gives the sum of the cohesive energy densities of solute and solvent minus twice their geometric mean, with the last term representing the energy gained in bringing the unlike molecules into contact. Cohesive energy has been equated with the energy of vaporization (1) and used to determine solubility parameters by:

$$\delta = \left[\frac{\Delta H^v - RT}{V}\right]^{1/2} \qquad \text{(Eq. 2)}$$

where $\Delta H^v$ represents heat of vaporization.

A solubility parameter of 9.5 $cal^{1/2}\ cm^{-3/2}$ was obtained for testosterone propionate (2) by a modification of the Chertkoff and Martin technique (3); this figure was confirmed later (4). Efforts at predicting solubilities in nonpolar solvents have been unsuccessful, however, and a reaffirmation of the value was sought.

## EXPERIMENTAL

**Materials**—Steroid alcohols[1] and testosterone propionate[1] were obtained from a commercial source. Methods of characterization and preparation of the remaining esters were described previously (5). Saturated hydrocarbons were purchased from various sources; purities were never less than 97%. Research grade cyclohexane[2] (minimum purity 99.99%) was used for vapor pressure determinations. Anisole and carbon tetrachloride were of reagent grade and were fractionally distilled before use. Solubilities in these solvents were determined using previously described techniques (2, 6), and the remaining solubilities were taken from the literature (2, 7) (Table I).

**Solubility Parameters**—Nonpolar solvent solubility parameters, calculated from Eq. 2, are given in Table I. Some were obtained from published heats of vaporization (8); the remaining values were calculated from vapor pressures (9), corrected using (10):

$$\Delta H^v = \Delta H^v_{app}\, e^{-mT} \qquad \text{(Eq. 3)}$$

where $\Delta H^v$ represents the true heat of vaporization, $\Delta H^v_{app}$ is the experimental value at temperature $T$, and $m$ is a constant. Polar solvent solubility parameters, taken from the literature (1), are

[1] Gifts from Organon Laboratories Ltd.
[2] British Drug Houses Ltd.