ment were then tested with a vibration analyzer[2]. The analyzer probe was touched to various parts of the apparatus that contact the dissolution flask, and the vibration displacement and frequency values were recorded and averaged to give an estimate of the magnitude of vibration. These data are given in Table I, together with dissolution times obtained for a lot of tolbutamide tablets USP. Using the "Vibration Severity Chart" supplied by the manufacturer of the vibration analyzer, we rated the mechanized apparatus "extremely smooth" and the nonmechanized apparatus "slightly rough." Sources of vibration in the nonmechanized unit were traced to the benchtop, floor, and water circulator motor, with the latter being the principal source. When the circulator motor was turned off, the apparatus was rated "very good."

It is apparent from Table I that the effect of vibration on the dissolution rate of tolbutamide tablets USP is quite pronounced when the basket is rotated at 150 r.p.m., but it is almost insignificant when the basket is rotated at 300 r.p.m. In fact, for this lot of tablets the dissolution time obtained with the nonmechanized apparatus at 150 r.p.m. is about equivalent to that obtained with the mechanized apparatus at 300 r.p.m.

Some insight into the effect of vibration may be gained from a dissolution time–revolutions per minute profile. The profile shown in Fig. 1 was obtained, using the mechanized apparatus, for the same lot of tablets for which data are presented in Table I. Note that the slope is quite steep at 150 r.p.m. but quite flat at 300 r.p.m. Since additional vibration has the same effect on dissolution as additional rotation speed, it becomes immediately apparent why the effect of vibration is much more pronounced at 150 r.p.m. than at 300 r.p.m.

We have found that the shape of the dissolution time–revolutions per minute profile varies considerably from product to product, and to a lesser extent, from lot to lot of the same product. Therefore, control of vibration is more important for some products than for others. Undoubtedly, the nature of ingredients and the disintegration characteristics of the formulation are important factors.

It is not the purpose of this communication to cast doubt on the value of the USP and NF rotating basket dissolution test. In fact, we believe that this test holds much promise for the control of lot-to-lot dissolution-rate uniformity. However, if meaningful interlaboratory or even intralaboratory comparisons are to be made using this test, such variables as the one we have discussed must be identified and controlled.

When establishing dissolution specifications for products using the rotating basket method, the data presented here suggest two courses of action: either vibration must be carefully controlled within a specified limit as defined by an objective vibration test procedure, or its effects must be reduced by rotating the basket at sufficient speed.

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Preparation and Characterization of Lincomycin Cyclamate

Keyphrases ☐ Lincomycin cyclamate—synthesis, characterization ☐ Cyclamate interference—lincomycin therapy

Sir:

In recent studies, small quantities of the synthetic sweetening agents, sodium or calcium cyclamate[1], were shown to reduce the absorption of the antibiotic lincomycin hydrochloride to 25–30% of control values obtained in the absence of these agents (1). This activity was observed during carefully controlled clinical pharmacology studies, in which blood levels and/or urinary excretion were measured, in the development of a pediatric syrup of this antibiotic. It was found that depression in absorption of lincomycin occurs not only when the cyclamate is present with the antibiotic in the syrup ingested by both adults and children but also when the antibiotic is taken as the syrup and the cyclamate is ingested in the form of a diet drink[2], and mixing of the two fluids occurs in the human stomach. One molar equivalent of cyclamate essentially produced maximum depression of absorption of lincomycin hydrochloride, whereas no interference was found with the absorption of tetracycline hydrochloride.

In view of the obvious hazard to lincomycin therapy posed by the apparent interference of common cyclamates, we investigated the possibility of a metathetic reaction leading to precipitation of lincomycin cyclamate. Lincomycin cyclamate was expected to be easily precipitated from aqueous media by analogy with the known sparingly soluble hexadecylsulfamate and octadecylsulfamate salts of lincomycin (2) and from the fact that cyclamate salts have been prepared and characterized from several widely used classes of drugs such as antihistaminic, autonomic, myospasmolytic, central stimulant, neuroleptic, antitussive, antibiotic, and local anesthetics (3).

To our surprise, no precipitate formed when nonsaturated aqueous solutions of equivalent quantities of lincomycin hydrochloride were treated with either sodium or calcium cyclamate. Slightly impure linco-

[1] Sucaryl.
[2] Such as Diet-Rite Cola or Like.

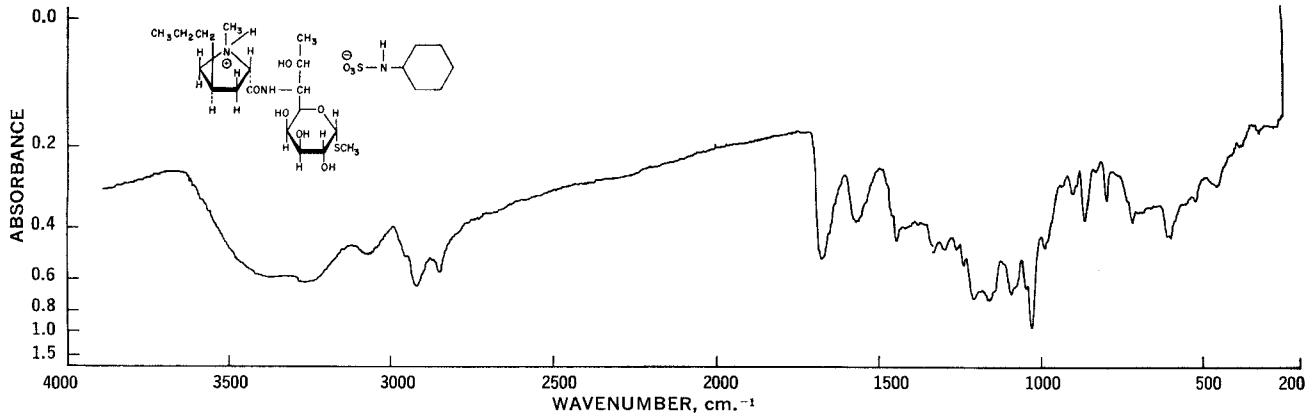

Figure 1—*Split mull IR spectrum (Perkin-Elmer 621 spectrometer) of lincomycin cyclamate dihydrate.*

mycin cyclamate, however, could be obtained as a waxy-white solid by slow, dropwise addition of a saturated aqueous solution of calcium cyclamate to a saturated aqueous solution of lincomycin hydrochloride. Solidification of the reaction mixture occurs suddenly, just short of complete addition of the equivalent quantity of calcium cyclamate. The precipitate is insoluble in excess saturated aqueous calcium cyclamate, but it is easily dissolved by water (solubility ~ 84 mg./ml.). It was possible to collect the lincomycin cyclamate at the stage of initial appearance of the waxy-white solid by treating the mixture with the minimal volume of absolute ethanol required to effect transfer. When, however, the preparation of lincomycin cyclamate was attempted from a concentrated solution of lincomycin HCl·H_2O in absolute ethanol (100 mg./1.5 ml.) by dropwise addition of a saturated aqueous solution of calcium cyclamate, no crystallization occurred on standing either at room temperature or at 0°, and no crystallization (neither lincomycin cyclamate nor calcium cyclamate) could be induced by further addition of absolute ethanol.

The lincomycin cyclamate prepared under these saturated aqueous conditions was characterized by mixed melting-point determinations and by comparison of IR spectra obtained from the same salt prepared under nonaqueous conditions. Lincomycin free base was generated from lincomycin HCl·H_2O (100 mg., 0.231 mmole) on treatment with excess aqueous am-

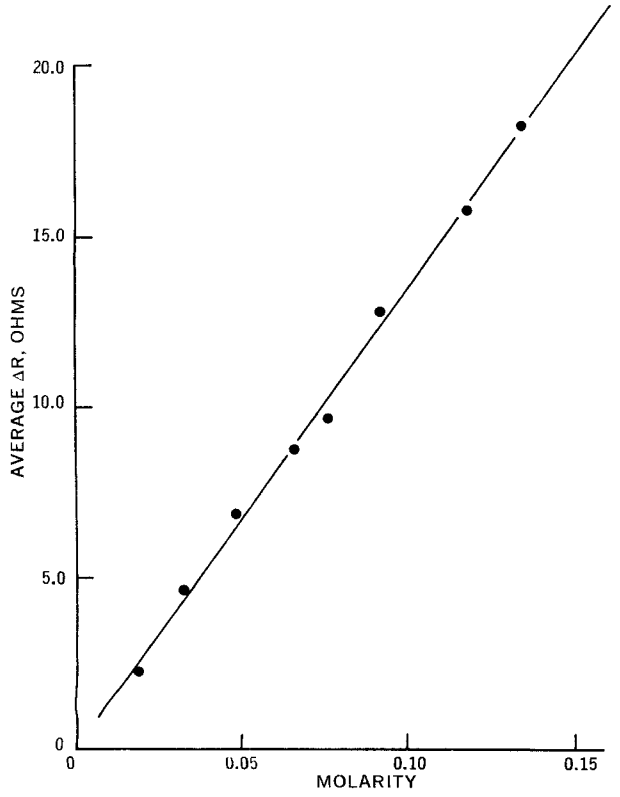

Figure 2—*Thermoelectric vapor phase osmometric measurements on individually prepared aqueous solutions of lincomycin cyclamate dihydrate at 37°.*

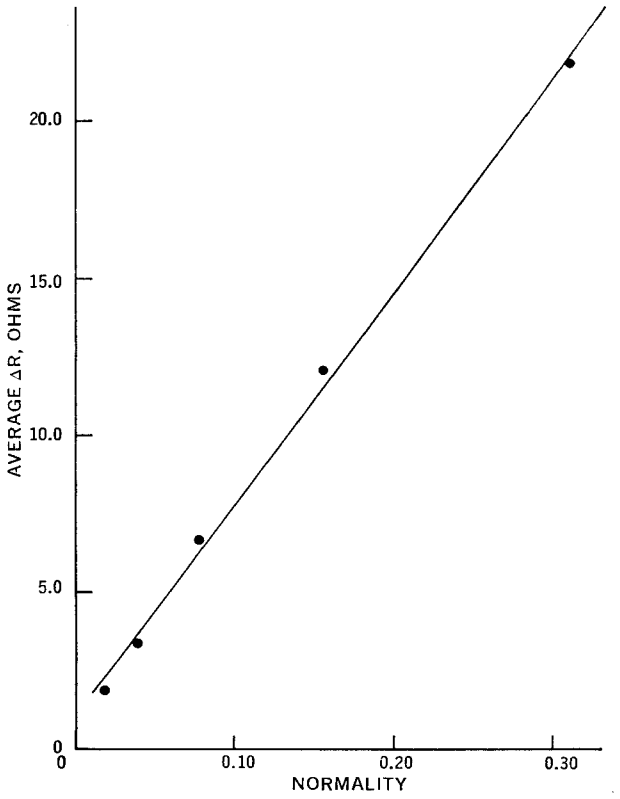

Figure 3—*Thermoelectric vapor phase osmometric dilution study of the effect of calcium cyclamate dihydrate on lincomycin cyclamate dihydrate at 37°. Dilution was followed from an aqueous solution 0.0163* M *(0.0490* N*) in calcium cyclamate dihydrate and 0.133* M *(0.265* N*) in lincomycin cyclamate dihydrate from an initial solution 0.314 total normality.*

monia and extracted with diethyl ether. After drying over anhydrous magnesium sulfate, the ethereal lincomycin solution was treated with a nearly saturated solution of cyclohexylsulfamic acid (42 mg., 0.231 mmole) in methyl ethyl ketone. Instant crystallization occurred during the addition. The crystals were collected, washed with diethyl ether, dried over P_2O_5, and found to melt at 149–151° (Kofler).

Anal.—Calcd. for $C_{18}H_{34}N_2O_6S \cdot C_6H_{13}NO_3S \cdot 2H_2O$: C, 46.36; H, 7.62; N, 6.76; S, 10.31. Found: C, 46.74; H, 8.14; N, 7.45; S, 10.49.

IR spectra (Fig. 1) of the lincomycin cyclamate dihydrate showed a broad band centered at 3400 cm.$^{-1}$ for ν_{O-H} from the water of hydration as well as from other OH groups within the lincomycin molecule itself and strong bands at 1165 and 1035 cm.$^{-1}$ for asymmetric and symmetric $\nu_{S=O}$ of the sulfonic acid moiety in the ionic form characterized by Detoni and Hadzi (4). These features are also consistent with $\nu_{O=H}$ at 3412 cm.$^{-1}$ and $\nu_{S=O}$ at 1168 and 1060 cm.$^{-1}$ found for calcium cyclamate dihydrate.

An attempt was made to prepare the anhydrous lincomycin cyclamate salt by subjecting the dihydrate to a pumping vacuum (0.1 mm. Hg) while heating the salt at 100° for 2–3 hr. No dehydration could be detected by comparison of IR spectral features. While these conditions have usually been satisfactory for dehydrating a wide range of salts (5), thermal gravimetric analysis (TGA) later showed no significant weight loss (2% up to 175°, probably due to surface moisture) by the material below 230°. An upper temperature limit is imposed by melting of the salt at 150°. We were also concerned about possible thermal degradation of the cyclamate salt, having observed a remarkably easy degradation of the hydrochloride salt (6) during evaporation of an aqueous ethanolic solution (pH 2) at 50° and 15 mm. Hg in a rotary evaporator. Differential thermal analysis (DTA) indicated the cyclamate salt to be much more stable than the hydrochloride and showed the following features: a small broad endothermic peak at 157° with no weight change (possibly a softening reaction) and large exothermic reactions accompanied by weight loss at 239, 323, and 506°. The sample was totally volatilized in air at 600°.

In view of these observations and our considerable difficulty in preparing lincomycin cyclamate, we conclude that the reported interference to absorption of lincomycin hydrochloride by common cyclamates does not involve a simple metathetic reaction. Since the next most likely cause of interference could arise from association of cyclamate anions with lincomycin cations in aqueous media, thermoelectric vapor phase osmometry (7, 8) was employed over the largest possible concentration range (Figs. 2 and 3) in an attempt to detect evidence of aggregation. In the absence of discontinuities in the curves of Figs. 2 and 3, it follows that no association of cyclamate with lincomycin ions occurs even in solutions slightly supersaturated with respect to lincomycin cyclamate (*e.g.*, 0.134 *M*, Fig. 2, and 0.133 *M*, Fig. 3). Other possibilities, therefore, apart from these simple physical phenomena must be considered to explain the apparent interference of common cyclamates to lincomycin therapy.

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Comparative Systemic Availability of Acetaminophen when Administered Orally as Such and as Acetophenetidin

Keyphrases ☐ Acetaminophen systemic availability—acetaminophen, acetophenetidin administration ☐ Systemic availability, correlation—acetaminophen-precursor administration

Sir:

Phenolic drugs are metabolized to glucuronides and sulfates in man and animals (1). The systemic availability of some of these drugs upon oral administration may be decreased appreciably by biotransformation in the gastrointestinal mucosa and during the "first pass" through the liver (2–4). Acetaminophen (4′-hydroxyacetanilide) is a widely used analgesic and antipyretic agent which is eliminated mainly by glucuronide and sulfate formation (5). The related compound acetophenetidin (4′-ethoxyacetanilide) is largely converted in the body to acetaminophen (6). If acetaminophen is metabolized appreciably during absorption, its systemic availability should be relatively increased by administering its precursor, acetophenetidin, which has its phenolic group blocked and therefore protected from conjugation in the gut wall.

Prescott *et al.* (7) determined acetaminophen concentrations in the plasma upon oral administration of 1.8 g. acetaminophen or acetophenetidin to groups of normal subjects. They also determined the total urinary