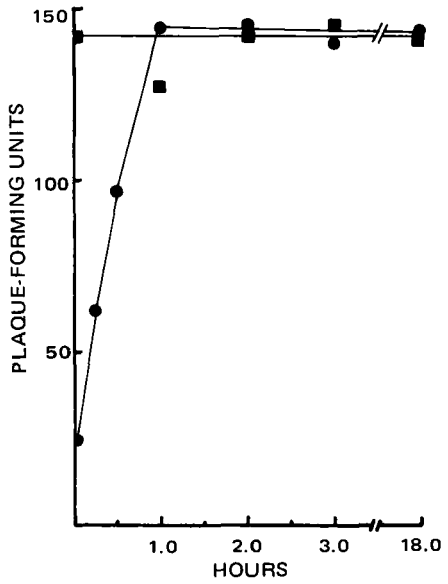

Figure 2—*Plot of time between inoculation with herpes simplex and treatment with gossypol (5 μg/ml)* versus *the plaque-forming units observed. Key:* ■, *control; and* ●, *gossypol treated.*

lar mechanism may be operative in viral inactivation, it does not appear likely due to the good activity of apogossypol.

An alternative mechanism of antiviral activity could be that these compounds bind to the virion envelope and cause the subsequent destruction of the integrity or loss of the envelope. If the membrane is the site of action, the basis for the selective toxicity to the viral particle might result from the structural differences between the envelope membrane of herpes and the outer membrane of the host cell (14). An alternative basis of the selective toxicity to the viral particle might be that the host cell has the capacity to repair membrane damage or inactivate gossypol and apogossypol. The viral particle, which is metabolically dormant, would not be expected to have either of these capabilities.

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Demonstration of Claimed "Controlled-Release" Properties of a Drug Formulation

Keyphrases □ Controlled-release properties of drug formulations—claimed *versus* actual, blood level profiles compared to "plain-release" blood level profiles □ Timed-release formulations—claimed *versus* actual "controlled-release" properties, blood level profiles compared to "plain-release" blood level profiles

To the Editor:

The concept of a "controlled-release" formulation of a drug is, by now, a familiar one. The basic idea is that of delaying or prolonging the *in vivo* release of an orally administered drug. Controlled-release formulations are often termed "slow release," "sustained release," or "delayed release." The advantages of such formulations are obvious; a sustained-release formulation, for example, which prolongs blood levels over a greater period and eliminates high peaks of drug concentration, allows the possibilities of less frequent dosing and the elimination of side effects related to peaks in the blood level profile.

Two questions might reasonably be asked concerning a purportedly controlled-release formulation. First, is it efficacious in the dosage schedule recom-

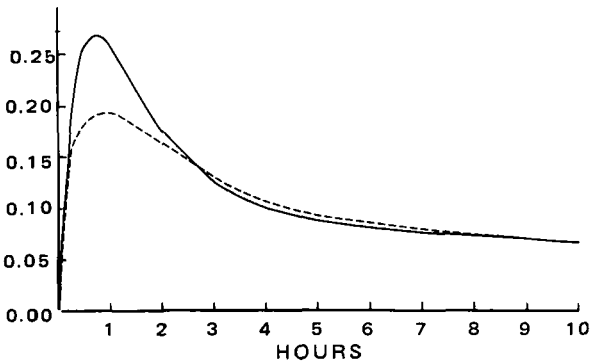

Figure 1—*Illustrative blood level curves. Key: – – –, controlled-release formulation; and —, plain-release formulation.*

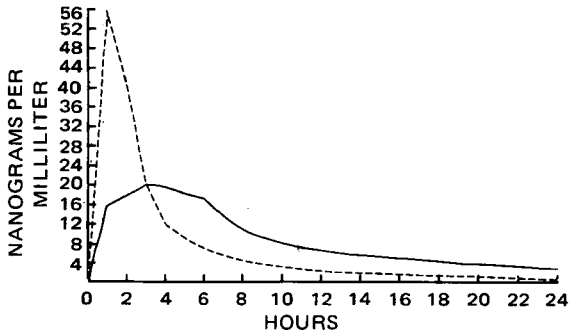

Figure 2—*Blood level curves from a 40-mg plain-release tablet of caramiphen (- - -) and from a 40-mg controlled-release formulation of caramiphen (—).*

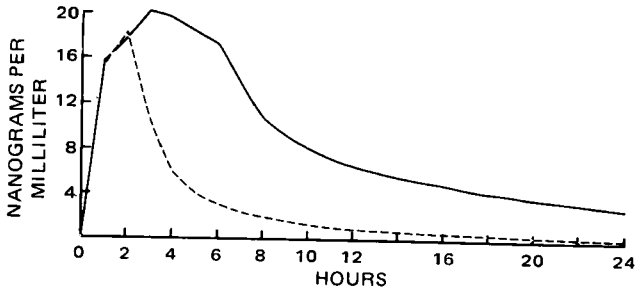

Figure 4—*Blood level curve from a 40-mg controlled-release formulation of caramiphen (—) and predicted blood level curve from a regimen of 11 mg of caramiphen at zero hr and 5 mg at 1 hr, both in plain-release tablets (- - -).*

mended? And second, does it indeed have the property of controlled release claimed for it? The fact that a once-a-day administration of a certain amount of drug in a controlled-release formulation proves to be as efficacious as a conventional regimen of the same amount of drug given in three divided doses taken over 24 hr is, in itself, no proof of controlled release. Figure 1 should make this clear. The single, plain dose might be highly effective therapeutically but never administered in this fashion because of, for example, the intolerable side effects associated with the high peak blood level. The purportedly controlled-release formulation might also be effective therapeutically in a once-a-day regimen without the accompaniment of side effects. However, one could hardly claim the controlled-release property for it on the basis of the blood level profile shown in Fig. 1. What appears to have happened is that the formulation simply makes the drug less available at the critical point where side effects might occur.

Apparently, the efficacy of a purportedly controlled-release formulation in the proposed regimen and its controlled-release character are independent questions requiring their own proof. Establishment of either one cannot be used to infer the presence of the other; the proof that a formulation possesses a controlled-release characteristic must be tackled directly. For example, if the drug in question generates a pharmacological response that can be measured with reasonable precision, a study measuring this response can be made the basis of a demonstration of the controlled-release property. In many cases, however, the most convenient approach will be through a pharmacokinetic study. A number of pharmacokinetic methods can be devised to demonstrate the controlled-release of a formulation; one that seems to represent the most generally satisfactory approach to the problem will be described here.

The method proposed is that of determining the regimen of divided doses to which the controlled-release formulation is equivalent in the sense that it generates an equivalent blood level profile over time. To illustrate the method, consider the blood level profiles (based on the mean from a number of subjects) obtained with two formulations of caramiphen: a 40-mg plain-release tablet and a 40-mg controlled-release formulation. Linear pharmacokinetics are assumed so that the predicted blood levels from any dose of caramiphen in the plain-release tablet can be obtained from the dotted line in Fig. 2 by scaling up or down by the appropriate factor.

One then determines what dose of plain-release drug given at $t = 0$ appears to match the beginning of the controlled-release blood level curve. Scaling the dotted line curve in Fig. 2, one finds that 11 mg given in a plain-release tablet appears to be a good match (Fig. 3). To match further the controlled-release blood level curve, one then finds that 5 mg in a plain-release form appears to be needed at 1 hr (Fig. 4). Further doses are added where required to match the controlled-release blood level curve until the allotted 40-mg dose is used up. The only principles involved are those of linear pharmacokinetics, involving scal-

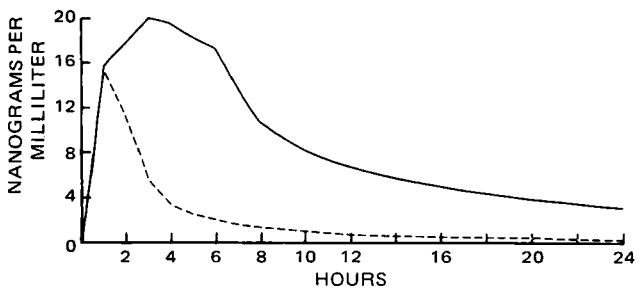

Figure 3—*Blood level curve from a 40-mg controlled-release formulation of caramiphen (—) and predicted blood level curve from 11 mg of caramiphen in a plain-release tablet administered at zero hr (- - -).*

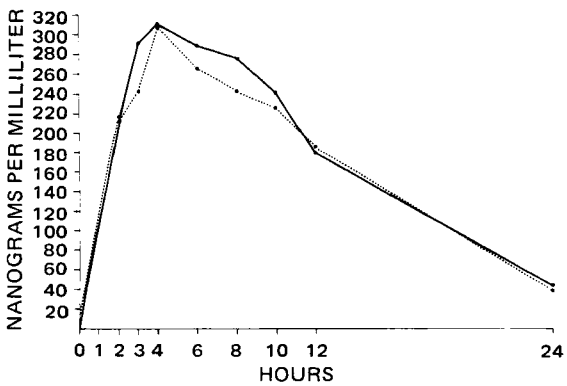

Figure 5—*Blood level curves from a 150-mg controlled-release formulation of phenylpropanolamine (—) and from a regimen totaling 150 mg of phenylpropanolamine given in various doses at 0, 1, 2, 3, 5, 6, and 7 hr (- - -).*

ing of curves, superpositioning, and adding of superposed curves.

Of course, one could fit a compartment model and proceed in a similar manner, but I have already expressed a preference for using simple empirical techniques (1). What is required to achieve the curve matching expeditiously is a small digital computer with an oscilloscope-type display[1]. One sets up the controlled-release blood level curve as background on the oscilloscope and then tries to match it by trial and error, which usually requires 5–10 min.

At this point, by *theoretical* pharmacokinetic computations, a regimen of plain-release doses has been derived which is predicted to match the controlled-release formulation with respect to its blood level curve. The next step is, of course, to verify the validity of these theoretical calculations with an actual comparative trial in human subjects. Figure 5 shows the actual mean blood level curves of phenylpropanolamine obtained in a crossover trial in 12 subjects. A controlled-release formulation of 150 mg was compared with the following regimen:

hours	dose, mg
0	52.4
1	21.4
2	23.8
3	23.8
5	9.6
6	9.6
7	9.4

This regimen was derived from pharmacokinetic computations of the type described. The blood level curves obtained in Fig. 5 appear to show a good match; apparently this regimen of divided doses does give rise to essentially the same blood level profile as the controlled-release formulation.

The question still exists as to whether the divided dose regimen is sufficiently dispersed over time to merit the title controlled release for the formulation that it appears to mimic. As an extreme example, the controlled-release description would probably not be merited for a formulation that appears to be equivalent to a divided dose regimen of 145 mg at zero hr and 5 mg at 1 hr. Obviously, some arbitrary rules are needed. Nevertheless, the proposed method offers a reasonable way of handling the problem of demonstrating controlled release.

So that no misunderstanding occurs, it should be noted that no claim is made that the divided dose regimen is a model of how the controlled-release formulation behaves *in vivo* but rather that it gives rise to blood levels equivalent to those generated by the controlled-release formulation.

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[1] A PDP-12 has been found ideal for this purpose.

Antitumor Agents XIV: Molephantinin, a New Potent Antitumor Sesquiterpene Lactone from *Elephantopus mollis*

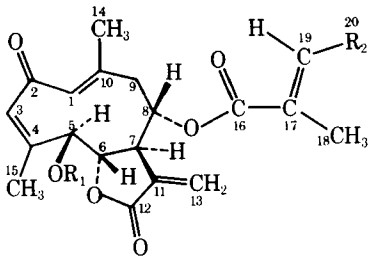
Keyphrases □ *Elephantopus mollis* H.S.K.—isolation and structure determination of molephantinin, antitumor activity □ Molephantinin—isolation, structure determination, and antitumor activity □ Antitumor agents, potential—molephantinin, constituent of *Elephantopus mollis* H.S.K. □ Structure-activity relationships—sesquiterpene lactones as antitumor agents

To the Editor:

We recently reported the isolation and structure determination of two novel cytotoxic germacranolides, molephantin (IV) (1) and phantomolin (2), from *Elephantopus mollis* H.S.K. This report[1] involves the isolation of an additional new sesquiterpene lactone, molephantinin (I), from the winter collection of this same plant. Molephantinin showed significant (T/C ≥ 125%) inhibitory activity against the Walker 256 carcinosarcoma in rats (T/C = 397%) at the 2.5-mg/kg level[2].

Molephantinin was isolated from the mother liquor after the removal of molephantin and phantomolin by silica gel column chromatography. Molephantinin, mp 223–225°, has the composition $C_{20}H_{24}O_6$ and shows an IR spectrum very similar to that of molephantin, indicating the presence of a hydroxy group (3420 cm^{-1}), a γ-lactone (1775 cm^{-1}), and the conjugated enone system (1713 and 1650 cm^{-1}). The NMR spectrum of molephantinin is superimposable with that of molephantin, except for the signal patterns in the acid portion of the ester. These differences were observed in molephantinin as the broad vinyl multiplets at δ 6.92 (1H, H-19) and the vinyl methyl multiplets at δ 1.83 (6H, H-18 and H-20), which are the typical signals for the tigloyl group (5, 6).

Added confirmation for these assignments was obtained by a comparison of the mass spectra of molephantinin and molephantin. The base peak in the mass spectrum of molephantinin is at *m/e* 83, due to



I: R_1 = H, R_2 = CH_3
II: R_1 = $COCH_3$, R_2 = CH_3
III: =O replaces R_1O ⟋ H, R_2 = CH_3
IV: R_1 = H, R_2 = H
V: R_1 = $COCH_3$, R_2 = H

[1] For Part XIII, see Ref. 3. For Part XII, see Ref. 2.
[2] Antitumor activity was assayed by Dr. I. H. Hall, Department of Medicinal Chemistry, School of Pharmacy, University of North Carolina at Chapel Hill, by a literature method (4).