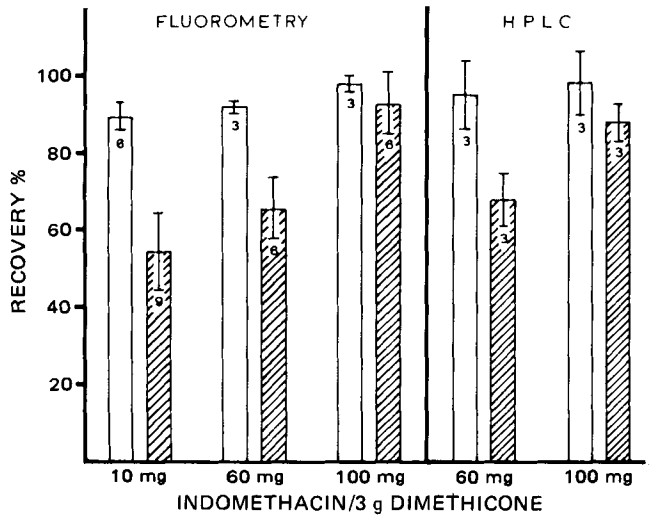

Figure 1—*Mean percentage recovery of indomethacin from dimethicone rods at different concentrations following ethylene oxide treatment (hatched bars). Standard deviations and the number of rods extracted in each group are shown. Results of gassed and ungassed rods at each indomethacin concentration were compared by t test analysis. This revealed no significant difference for the rods containing 100 mg of indomethacin/mixture. For the 60- and 10-mg/mixture groups, however, p values were <0.01 and <0.001, respectively.*

the 10 and 60 mg/mixture rods (Fig. 1). There was also a slight reduction in the recoveries for the 100 mg/mixture rods, but this difference was not significant, as determined by *t* test analysis, from the ungassed rods.

Continuous scan recording by the fluorometer showed no change in the shape of the curves obtained from the analysis of extracts of gassed rods, and no additional peaks were seen in the trace recordings of the HPLC analysis.

DISCUSSION

These results provide evidence that ethylene oxide treatment reduces the extraction into alcohol of a common nonsteroidal anti-inflammatory drug incorporated into a dimethicone delivery system. This effect was dependent upon the concentration of the drug, with the lower doses (10 and 60 mg/mixture) being most affected. For the rods made from 100 mg indomethacin/mixture, over 90% of the drug was recovered after gassing, indicating that rods made to contain the drug at this concentration would be suitable for studies of indomethacin release rates from dimethicone rods placed in the body. The similarity in profiles of the extracts from the gassed and nongassed rods (continuous fluorometric scan and HPLC tracings) suggest that no alteration in the qualitative composition of the extracts occurred. The reasons for the reduced recoveries of indomethacin at the two lowest concentrations were not investigated here. One possibility is that at low drug concentrations, a greater matrix volume would be unoccupied by the drug and is available to be taken up by the gas. This, in turn, might alter the diffusion properties of the matrix or chemically interfere with the drug, thereby reducing its extraction into alcohol.

It would be valuable to know if other nonsteroidal anti-inflammatory drugs, and those steroids that are currently being used in conjunction with dimethicone systems (4, 5, 6), are affected by ethylene oxide gassing.

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COMMUNICATIONS

Model-Independent Steady-State Volume of Distribution

Keyphrases □ Pharmacokinetics—evaluation of model-independent steady-state volume of distribution □ Drug disposition—first-order disposition rates, evaluation of model-independent steady-state volume of distribution □ Models, pharmacokinetic—methods to evaluate model-independent steady-state volume of distribution

To The Editor:

Recently, pharmacokinetic methods have been proposed to evaluate model-independent input and disposition parameters for drugs exhibiting first-order disposition rates (1–4). The use of these statistical moment parameters is appealing, not only because of the relatively simple calculations involved, but also because the parameters determined are independent of any modeling assumptions, which greatly facilitates cross-study comparison of drug disposition. For example, Benet and Sheiner (5) have compiled volume of distribution steady-state (Vd_{ss}) data for numerous drugs using statistical moment analysis. However, as proposed (4), the method is valid only for single dose instantaneous input data and will result in an overestimation of Vd_{ss} when applied to data obtained after infusion or multiple dose input. The purpose of this communication is to report a simple method to obtain Vd_{ss} values from multiple intravenous bolus and/or infusion data.

For a drug administered by bolus injection, a single distribution–elimination rate parameter, the mean residence time (MRT_{iv}), can be evaluated using statistical moment analysis (1). The MRT_{iv} describes the average time a drug molecule spends in the body and is determined

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by dividing the area under the concentration multiplied by time–time curve [area under the moment curve ($AUMC$)] by the area under the concentration–time curve (AUC):

$$MRT_{iv} = \frac{AUMC_{iv}}{AUC_{iv}} \quad \text{(Eq. 1)}$$

As shown previously by Benet and Galeazzi (4), a model independent distribution volume (Vd_{ss}) may be determined from the dose (D), MRT_{iv}, and AUC_{iv} as follows:

$$Vd_{ss} = \frac{D(MRT_{iv})}{AUC_{iv}} = \frac{D(AUMC_{iv})}{(AUC_{iv})^2} \quad \text{(Eq. 2)}$$

If the same dose (D) is administered as an infusion over a time (t') or is divided into increments ($D_1, D_2, \ldots D_n$) and administered as a combination of infusions and/or boluses at different times ($T_1, T_2, \ldots T_n$), the area under the curve (AUC_{total}) will equal the AUC_{iv}; but the $AUMC_{total}$ will be greater than the $AUMC_{iv}$, resulting in an overestimation of Vd_{ss} if $AUMC_{total}$ is used in Eq. 2. For a case where the drug is administered as a single infusion rather than a bolus, the MRT_{total} and the $AUMC_{total}$ are easily corrected, since the infusion will increase the MRT_{iv} by $0.5t'$ (6), and:

$$AUMC_{iv} = AUMC_{total} - AUC_{iv}(0.5t') \quad \text{(Eq. 3)}$$

When multiple dosing occurs, the correction is somewhat more complex, since there is a delay (T) in the input of a fraction of the dose. Assuming there is no previous dosing, the delay time will increase the MRT_{iv} by T if administered as a bolus and by $0.5t' + T$ if administered as an infusion, and:

$$AUMC_{iv} = AUMC_{total} - AUC_{iv}(0.5t' + T) \quad \text{(Eq. 4)}$$

The general form for n bolus and/or infusion doses then becomes:

$$AUMC_{iv} = \sum_{i=1}^{n} AUMC_i - \sum_{i=1}^{n} AUC_i(0.5t_i' + T_i) \quad \text{(Eq. 5)}$$

where: $t_i' = 0$ for a bolus dose and $T_1 = 0$.

Dividing both sides of Eq. 5 by AUC_{iv} (the total AUC calculated), and recognizing the ratio of the individual AUC_i's to AUC_{iv} is the fraction of the total dose administered (F_i), one obtains:

$$MRT_{iv} = MRT_{total} - \sum_{i=1}^{n} F_i(0.5t_i' + T_i) \quad \text{(Eq. 6)}$$

Equation 6 may be used to correct total moment data for use in Eq. 2, even when a bolus is administered during an infusion. Although it is not valid if residual drug is present prior to characterization of the concentration–time curve, corrections for the residual drug are possible in certain instances. One may be tempted to correct for oral dosing by adding $1/K_a$ to the summation term in Eq. 6, but the fraction of the oral dose absorbed must be known as well as K_a. Finally, calculation of $AUMC_{total}$ and AUC_{total} are subject to extrapolation errors as described previously (3, 4), so it is advisable to obtain data which will allow excellent characterization of the terminal elimination rate constant after the last dose increment is administered, or to collect samples until the concentration of drug is essentially zero.

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Tampon Leachable Substances: Acute Toxicity

Keyphrases □ Tampons—leachable substances, acute toxicity □ Toxicity, acute—tampon leachable substances, intramuscular implantation in rabbits □ Inhibition of cell growth—acute toxicity of tampon leachable substances □ Dehydration—tissue response, acute toxicity of tampon leachable substances

To the Editor:

The use of tampons for the control of menstrual flow has been associated with the induction of vaginal ulcerations, mucosal changes, and toxic shock syndrome. The evidence for those clinical phenomena has been reviewed recently (1), emphasizing the role of dehydration and alteration of calcium levels in the vaginal tissue as important mechanisms in the induction of vaginal ulceration. Since we are not aware of any reports on the potential toxicity of leachable substances of tampons, two acute toxicity tests were performed on regular and superabsorbant tampons available commercially. The tests performed were: a tissue culture inhibition of cell growth test on aqueous extracts (23°) of whole tampons (Table I); and a 7-day intramuscular implantation test in rabbits using (*a*) the absorbant material of the tampons (excluding the casing and fibrous material), (*b*) partially hydrated absorbant material, and (*c*) fibrous material (excluding casing and absorbant material (Table II).

The decrease in the gross rating of the muscle implant of the partially hydrated tampon material as compared to the dry material implant was consistent with the generally accepted conclusion that dehydration is a major factor in the initiation of vaginal ulceration. Also, the soluble, leachable components of the tampons tested have a significant cellular toxicity at concentrations well below that which might be expected in vaginal secretions adjacent to a tampon. The tissue culture test covers a period of time (72 hr) of usual tampon usage, and several tampons are frequently used in that period. It should also be noted that there was a significant concentration-dependent response for both extracts and that the highest concentration tested was 50% with respect to the original extract.

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