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Influence of Ethylene Oxide Exposure on the Extraction of Indomethacin from Dimethicone Polymeric Rods

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ABSTRACT □ Dimethicone polymeric rods were made to contain 0.3, 2.0, or 3.3% by weight of indomethacin. For each different loading of indomethacin, some of the rods were treated with ethylene oxide at 55° for 1 hr, while others were not exposed to the gas. Treated and untreated rods were sliced, placed in ethanol to extract the indomethacin, and the concentrations of indomethacin in the extracts determined by fluorometry and high-performance liquid chromatography (HPLC). After ethylene oxide treatment, the quantity of indomethacin in the extracts was significantly reduced in rods containing 0.3 and 2.0% indomethacin. For the rods containing 3.3% indomethacin, the recovery of the drug from treated rods was not significantly different from those not exposed.

Keyphrases □ Ethylene oxide—extraction of indomethacin from dimethicone polymeric rods □ Indomethacin—dimethicone polymeric rods, influence of ethylene oxide exposure □ Polymeric rods—dimethicone, ethylene oxide exposure on extraction of indomethacin □ Fluorometry—determination of influence of ethylene oxide exposure on the extraction of indomethacin from dimethicone polymeric rods □ High-performance liquid chromatography—determination of influence of ethylene oxide exposure on the extraction of indomethacin from dimethicone polymer rods

The development of simple systems or devices for drug delivery over extended periods has potentially wide usage, especially for delivery of compounds to selected sites in the body. In this regard, experiments have been performed with a system which can provide a sustained release of nonsteroidal anti-inflammatory drugs such as indomethacin or naproxen from dimethicone polymeric rods (1). In these and other studies (2, 3) the quantity of drug released *in vivo* is determined by measuring the residual amount of drug in the rods at various time periods and subtracting it from values from similar rods prepared in an identical manner but which were not placed in the body. The measurements are performed on ethanolic or methanolic extracts of the rods.

Before being fitted into the body, such rods must be sterilized. Since autoclaving and chemical methods (such as placing in aqueous ethanol) appear unsuitable for this system, ethylene oxide gas treatment has been used.

The present study indicates that by using this method of sterilization, there is a decrease in the percentage of indomethacin that can be extracted into ethanol from rods containing the drug at low concentrations (<3% w/w).

EXPERIMENTAL

Indomethacin[1] was recrystallized, dried, and either 0, 10, 60, or 100 mg was thoroughly mixed with 3 g of dimethicone[2]. Following the addition of catalyst (15 mg) the different mixtures were forced into vinyl tubing (french gauge 5, 1-mm i.d.)[3] and allowed to polymerize. Rods of 1-cm length were cut and weighed and either stored at room temperature or subjected to ethylene oxide exposure (1.2–1.4 g/liter) in a stainless steel sterilizer[4]. In this apparatus the gas was released from ampuls into a chamber initially evacuated to 150 mm Hg. Following exposure to the gas for 1 hr at 55°, the rods were aerated for at least 12 hr and left for 2 days at room temperature.

Rods containing indomethacin were weighed, cut into thin slices, and the drug extracted with ethanol (2 ml/day for 4 days). The amounts of indomethacin in the extracts were determined by fluorometry and HPLC with standard solutions of indomethacin prepared from the recrystallized compound. For the fluorometric analysis, samples were assayed in duplicate using a spectrophotofluorometer[5] with an excitation wavelength of 295 nm and an emission wavelength of 361 nm. Continuous scan recordings over an emission range of 300 to 450 nm (constant excitation wavelength of 295 nm) were also made of certain extracts of the gassed and nongassed rods. For HPLC, 10 μl samples were injected into a C18 μ Bondapak column[6] with a mobile phase of methanol–50 m*M* KH_2PO_4 (3:1), pH 6.72, and a flow rate of 2 ml/min. The UV absorbance at 230 nm of the column eluate was continuously recorded with a variable wavelength UV detector[6]. Heights of the peaks corresponding in position to the indomethacin standards were measured to determine the amounts of indomethacin in the extracts. These amounts, compared with those determined to be present initially on the basis of the quantity of indomethacin in the mixture and the weight of each rod, were used to calculate percentage recoveries.

RESULTS

For the rods not subjected to ethylene oxide exposure, over 90% of the incorporated indomethacin was recovered into ethanol when measurements on the extracts were made by fluorometry (Fig. 1). This was confirmed by HPLC of the extracts of rods made from the 60 and 100 mg/mixture. (The HPLC system used did not allow a reliable measurement of indomethacin in the extracts obtained from the 10 mg/mixture rods as the peaks assigned to indomethacin were not sufficiently large to be accurately quantitated.) Following ethylene oxide treatment, however, the recovery of indomethacin into alcohol was significantly reduced for

[1] Sigma Chemical Co., St. Louis, Mo.
[2] Silastic, 382 medical grade elastomer, Dow Corning Corp., Midland, Mich.
[3] Latex Products Pty.
[4] Victoria MK II, Medical Electronics Ltd, U.K.
[5] Aminco-Bowman, Model 768 G, American Instrument Co., Silver Spring, Md.
[6] Waters Associates, Milford, Mass.

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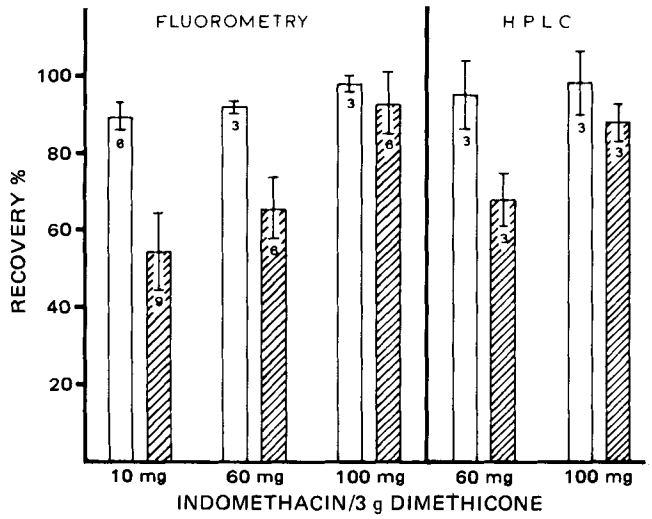

Figure 1—*Mean percentage recovery of indomethacin from dimethicone rods at different concentrations following ethylene oxide treatment (hatched bars). Standard deviations and the number of rods extracted in each group are shown. Results of gassed and ungassed rods at each indomethacin concentration 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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