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Dosage Form Index: An Objective Criterion for Evaluation of Controlled-Release Drug Delivery Systems

F. THEEUWES ˣ and W. BAYNE

Abstract □ A dimensionless parameter, the dosage form index (DI_τ), is proposed for evaluating the performance of drug delivery systems. The index is defined as the ratio of the maximum to minimum concentrations of the drug in plasma within each interdose interval (in hours), τ, during repetitive administration of the dosage form in the quasisteady state. Dosage form indexes can be averaged among subjects or within subjects at successive time periods to arrive at a mean value. As an example, two GI therapeutic systems—the 15- and 20-mg/hr acetazolamide systems that deliver drug at constant rates for 6 and 12 hr and contain 125 and 250 mg, respectively—were compared in normal subjects with a commercial sustained-release product containing 500 mg of acetazolamide. The dosage form index, DI_{24}, was 4.9 for the sustained-release dosage form and 3.2 for the 20-mg/hr system; DI_{12} was 1.6 for the 15-mg/hr system.

Keyphrases □ Drug delivery systems—sustained-release product and 15- and 20-mg/hr GI acetazolamide systems compared in humans, dosage form index suggested as evaluating parameter □ Dosage form index—suggested as evaluating parameter for drug delivery systems, sustained-release product and 15- and 20-mg/hr GI acetazolamide systems compared in humans □ Acetazolamide—sustained-release product and 15- and 20-mg/hr GI drug delivery systems compared in humans, dosage form index suggested as evaluating parameter □ Carbonic anhydrase inhibitors—acetazolamide, sustained-release product and 15- and 20-mg/hr GI drug delivery systems compared, humans

Optimum therapy with repetitive administration of conventional dosage forms (*e.g.*, injectables, liquids, or tablets) can classically be pursued by dosage scheduling. The aim of this process is to maintain drug concentrations in a therapeutic range, above the minimum effective concentration and below the toxic concentration.

The time course of systemic drug concentrations following repetitive dosing of intravenous injections and tablets, based on different absorption and elimination rate constants, was described mathematically using one-compartment and multicompartment pharmacokinetic models (1–3).

BACKGROUND

To discuss optimum drug dosing, the therapeutic index (TI) should be defined in terms of plasma concentrations (4) rather than dose (5):

$$\mathrm{TI} = \frac{C^*_{max}}{C^*_{min}} \qquad \text{(Eq. 1)}$$

where C^*_{max} and C^*_{min} are the maximum and minimum desired plasma concentrations, respectively, and must be defined further for each specific drug in relation to pharmacological responses.

Dosage scheduling should be carried out at a frequency such that the ratio of maximum to minimum plasma concentrations is less than TI and at a dose of sufficient magnitude to yield effective levels.

For a linear, one-compartment system with repetitive intravenous injections at pseudo-steady state, the ratio of maximum to minimum plasma concentrations is given by:

$$\frac{C_{max}}{C_{min}} = e^{k\tau} \qquad \text{(Eq. 2)}$$

where k is the drug elimination rate constant, and τ is the dosing interval. The C_{max}/C_{min} ratio has been called (1) Q_{ext}, the ratio of asymptotic extreme concentrations within a dosing interval of the multiple-dose curve. When the therapeutic index (TI) is known, the proper dosage interval must then be dictated by:

$$e^{k\tau} \leq \mathrm{TI} \qquad \text{(Eq. 3)}$$

or:

$$\tau \leq t_{1/2}\frac{\ln \mathrm{TI}}{\ln 2} \qquad \text{(Eq. 4)}$$

For TI = 2, the dosing interval should maximally be equal to the biological half-life of the drug. For drugs with a half-life of less than 12 hr and a low therapeutic index, proper dosage schedules are inconveniently frequent. To alleviate these problems, therapeutic systems were developed (6–8).

Therapeutic systems are a class of dosage forms designed to improve drug therapy through controlled administration of drug substances, in time and space, to elicit the optimum sum total of pharmacological response. They are specified not by content, size, or shape but by function: the rate at which they deliver drug *in vivo* and the duration for which they do so.

The GI therapeutic system is a new oral dosage form designed to control plasma drug concentrations for one area of application. The system's delivery rate profile provides one extra degree of freedom in addition to scheduling to arrive at optimum therapy. The selection of the system's delivery rate characteristic allows the interval τ to be a convenient time period that is much less dependent on $t_{1/2}$ and TI, as was the case classically.

GI therapeutic systems are constructed according to elementary osmotic pump technology (9). This osmotic system was developed as an oral dosage form because of its desirable delivery rate characteristics (9). The rate is predictable, essentially constant during most of the drug release process, independent of pH and GI motility, and adjustable so that it can be of sufficient magnitude to be of interest as an oral dosage form.

The dosing interval for the GI therapeutic system must also permit the resulting ratio of the maximum to minimum plasma drug concentrations to be smaller or equal to TI. This ratio at pseudo-steady state on repetitive dosing of the system is different from Q_{ext} as defined for conventional dosage forms (1) and is now a function of the dosage form characteristics. Therefore, it is defined as the dosage form index, DI_τ. The dosage form index is a function of the intrinsic pharmacokinetic properties of the drug (*e.g.*, absorption, distribution, and elimination), the dosing interval, τ, and the dosage form delivery rate. At equal dosing intervals, two dosage forms can be compared. The system with the lowest DI may be superior therapeutically. The dosage form index can be used also as a criterion to select the optimum dosage form and dosing interval.

In a previous study of acetazolamide in humans (4), the therapeutic index, defined in terms of plasma concentrations, was given as:

$$TI = \frac{120\ \mu M}{45\ \mu M} = 2.7 \qquad \text{(Eq. 5)}$$

At a plasma acetazolamide concentration of 120 μM, noticeable impairment of carbon dioxide transport by the red cells is expected since 96% of their carbonic anhydrase activity is inhibited. However, 45 μM or 10 μg/ml was an adequate concentration for lowering intraocular pressure. In the same work (4), plasma concentration profiles were calculated as described by Dost (2) for a regimen of 250-mg acetazolamide tablets four times a day. This regimen was considered to produce an adequate therapeutic effect, and the dosage form index was 2.7, *i.e.*, equal to the therapeutic index.

More severe side effects may occur on administration of conventional acetazolamide tablets at twice the daily dose than with a sustained-release form of the drug[1] (10). The discontinuation rate was 47% on dosing 250-mg tablets four times a day *versus* 11% on dosing the sustained-release form (500 mg) once a day, while the efficacies were comparable.

Since the 500-mg sustained-release dosage form, once a day regimen was believed to be the optimum treatment, it was compared with two types of acetazolamide GI therapeutic systems on the basis of the dosage form index, plasma concentrations, and urinary excretion in normal human volunteers.

EXPERIMENTAL

The dosage forms investigated were a sustained-release dosage form containing 500 mg of acetazolamide, delivering the drug in quasiexponential declining fashion by *in vitro* tests, and 15- and 20-mg/hr acetazolamide GI therapeutic systems (9), delivering 70% of their total content at zero order by *in vitro* tests. The two GI systems contained a total of 125 and 250 mg of acetazolamide and delivered their contents over 6 and 12 hr, respectively.

The 6-hr system was administered twice a day. The 12-hr system and the sustained-release dosage form were given once a day, and both were studied in eight volunteers in a crossover study. Five of the eight volunteers also received the 6-hr system. Each dosage form was administered for up to 10 days to allow blood sampling during successive periods at steady state. Steady state was verified by sampling blood at frequent intervals during Days 1, 3, and 10.

The standard deviation is defined by:

$$SD = \left(\frac{\sum^{n} (X_i - \overline{X})^2}{(n-1)} \right)^{1/2} \qquad \text{(Eq. 6)}$$

where $\overline{X}$ is the arithmetic mean of the series of n observations X_i.

[1] Diamox Sequel, Lederle Laboratories, Division of American Cyanamid Co., Pearl River, NY 10965.

Plasma samples were analyzed according to a recently published high-speed liquid chromatographic method (11).

A specific liquid chromatographic method was developed for urine. To 1 ml of urine was added 200 μl of a stock solution (0.16 mg/ml) of sulfadiazine[2] in 0.1 M phosphate buffer (pH 7), followed by 1 ml of 2.0 M acetate buffer (pH 4.5). The aqueous solution was extracted twice with 10 ml of ether–methylene chloride–isopropyl alcohol (6:4:2) (12). The combined organic extract was then extracted with 2 ml of 1 M carbonate buffer (pH 11).

The organic phase was discarded, and 700 μl of acetic acid was added to the aqueous phase. The aqueous phase was extracted with 10 ml of the mixture of organic solvents described. The aqueous phase was discarded, and the organic phase was then evaporated to dryness in a nitrogen stream at 40°. The residue was reconstituted in 200 μl of 0.01 N NaOH.

The reconstituted extract was injected onto a high-pressure liquid chromatograph; the chromatographic column contained an octadecylsilane monolayer bonded to a microparticulate silica support[3], with 2% dimethylformamide in 0.05 M phosphate buffer (pH 6.2) as the mobile phase. The flow rate was maintained at 2 ml/min with a constant-flow reciprocating pump[4]. Acetazolamide and sulfadiazine were detected in the eluant using a high-pressure mercury source[5] at 254 nm. The retention times for sulfadiazine and acetazolamide were 10.5 and 13.5 min, respectively.

Standard curves were constructed with varying amounts of acetazolamide (1–62.5 μg) and a constant amount of sulfadiazine (32.5 μg) per milliliter of urine. To determine acetazolamide concentrations in urine, a known amount of sulfadiazine was added, and the measured response ratios were obtained and converted to concentrations based on the standard curve. Chromatograms from blank samples (before acetazolamide administration) showed no interfering peaks with the retention times of acetazolamide or the internal standard. The absolute extraction efficiency of the method was approximately 80% for both acetazolamide and sulfadiazine.

RESULTS

Plasma Concentrations of Acetazolamide—The average plasma concentrations obtained from eight human subjects following acetazolamide administration *via* the sustained-release dosage form and 12-hr system once a day are shown in Fig. 1. Also shown are the average plasma concentrations for five subjects following administration of a 6-hr system twice a day. A continuing increase in plasma concentrations on administering the 6-hr system on Day 1 was due to the twice a day administration schedule. No 6-hr system was administered on the second half of Day 10. The data in Fig. 1 show that the dosage form and regimen combination of the 6-hr system twice a day resulted in the least variable plasma concentration profiles at quasisteady state.

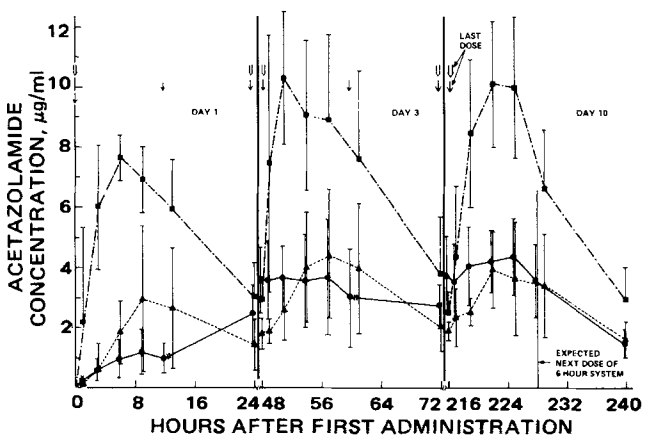

Figure 1—*Average plasma acetazolamide concentrations (±SD) in normal human subjects following administration of the sustained-release dosage form dosed once a day at ⇓, n = 8 (■); the 6-hr system dosed twice daily at ↓, offset 0.2 hr, n = 5 (●); and the 12-hr system dosed once a day at ⇓, n = 8 (▲).*

[2] K & K Laboratories, Plainview, N.Y.
[3] μBondapak C_{18}, Waters Associates, Milford, Mass.
[4] Model 6000, Waters Associates, Milford, Mass.
[5] Varian Instruments Division, Palo Alto, Calif.

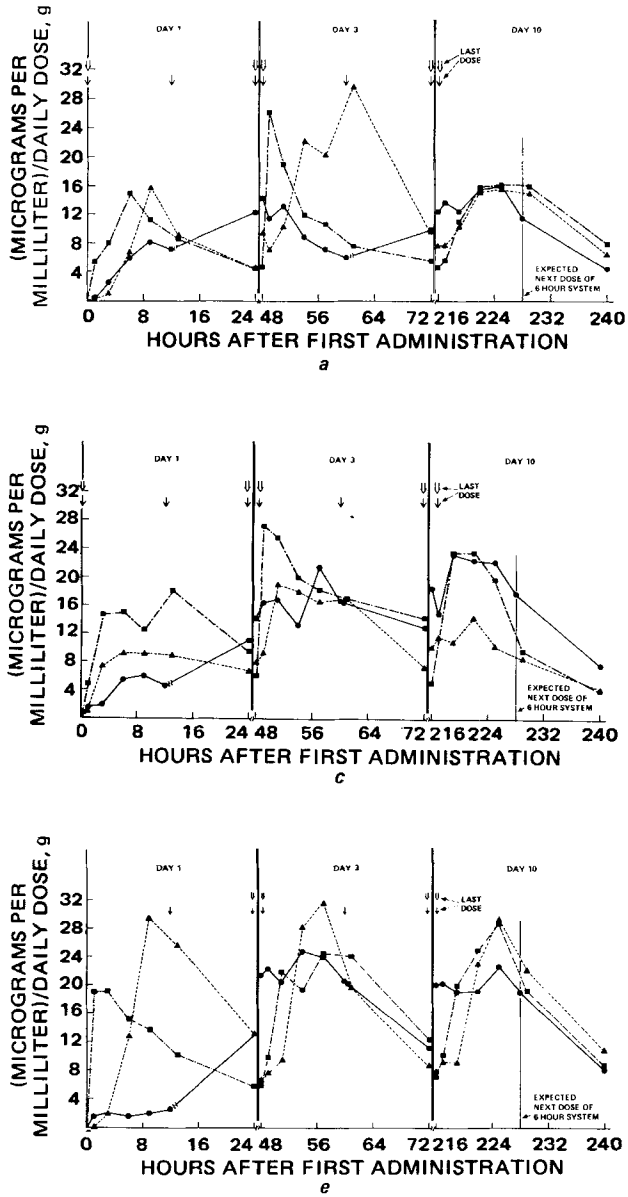

Figure 2—*Normalized plasma acetazolamide concentrations in normal human subjects following administration of three dosage forms. Key: a, Subject 287; b, Subject 337; c, Subject 263; d, Subject 297; and e, Subject 386. See Fig. 1 for definition of symbols.*

For each of the five subjects receiving each of the three dosage forms, the plasma concentrations were normalized to the daily dose (Fig. 2). Through normalization, plasma concentrations were calculated that would be obtained if 1 g of daily dose were administered from each of the dosage forms to the subjects, behaving as linear systems. The data were calculated by multiplying the actual plasma concentrations obtained following administration of the sustained-release dosage form once a day by two and by multiplying the plasma concentrations following administration of a 6-hr system twice a day and a 12-hr system once a day by four.

The average normalized plasma concentrations are shown in Fig. 3. The areas under the normalized plasma concentration–time curves (*AUC*) at steady state for each dosage form were calculated and averaged over all subjects for Days 3 and 10 (Fig. 4). The lack of significant difference in normalized areas under the plasma concentration–time curves indicates that the drug was absorbed from each dosage form to the same extent. This conclusion was supported by the urinary excretion data.

Urinary Excretion of Acetazolamide—Following administration of each dosage form, the urinary excretion of acetazolamide over 24 hr was determined for each subject. The 24-hr urinary recovery was averaged over all subjects for each dosage form as a percent of the daily dose and plotted as a function of time (Fig. 5).

The percent of the total dose administered over 10 days during each treatment recovered in the urine was averaged for all subjects and plotted in Fig. 6. On the average, 63% of the drug was excreted with each dosage form.

Dosage Form Indexes—Dosage form indexes were calculated for the sustained-release dosage form and the 12-hr system as the ratios of the maximum to minimum plasma concentrations encountered in a 24-hr dosing period during Days 3 and 10. For the 6-hr system, the index is the ratio of maximum to minimum plasma concentrations encountered in the 12-hr steady-state interval on Days 3 and 10, averaged over all

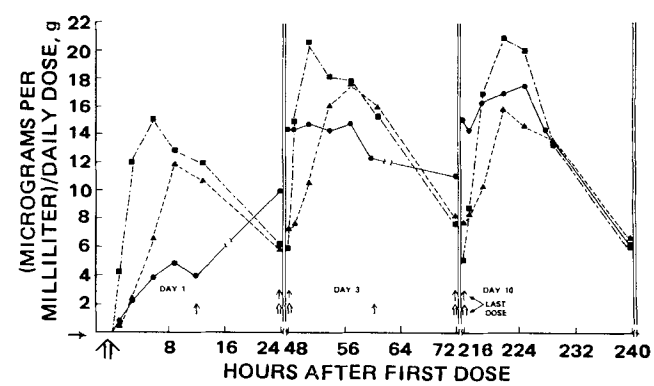

Figure 3—*Averaged normalized plasma acetazolamide concentrations in normal human subjects following administration of three dosage forms. Key: see Fig. 1.*

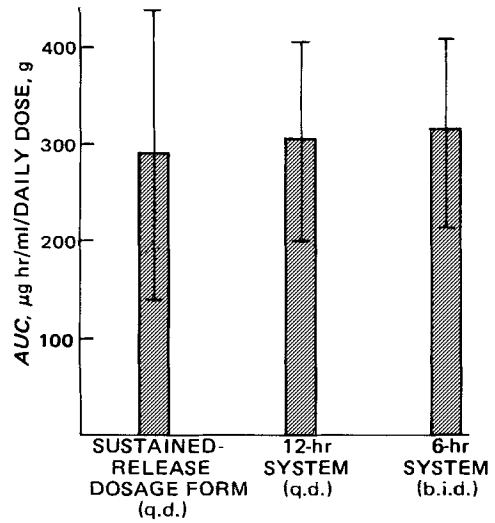

Figure 4—*Area under the normalized plasma concentration–time curves (±SD) averaged for all subjects on Days 3 and 10 (n = 10 for 6-hr system, n = 15 for 12-hr system, and n = 14 for sustained release).*

subjects. Since only one cycle of detailed plasma data was taken per day and per dosage form for all three dosage forms, one measure of the dosage form index was obtained per dosage form and per day. The averages of the dosage form indexes over all days and subjects are plotted in Fig. 7. The standard deviation indicates the variation from the mean over all subjects on Days 3 and 10.

The therapeutic value of a dosage form and schedule is expected to be greater when the dosage form index is small compared to the therapeutic index. By definition of the therapeutic index (Eq. 1), side effects are more likely to occur when DI_τ is large compared to TI, provided the minimum concentration, C_{min}, observed during treatment is larger or equal to C^*_{min}, the minimum effective concentration. The ratio:

$$SI = \left(\frac{DI_\tau}{TI}\right)_{C_{min}=C^*_{min}} \quad \text{(Eq. 7)}$$

can be defined as the side-effects index (SI), indicating the absence of side effects for SI < 1 and an increasing number and/or severity of side effects for SI > 1.

The dosage form indexes demonstrate that, relative to the sustained-release dosage form administered once daily, a decrease in the side-effects index was obtained by a factor of 1.5 for the 12-hr system dosed once a day and by 3.2 for the 6-hr system dosed twice a day. Figure 7 shows that an improvement was obtained by selecting the 12-hr system over the sustained-release dosage form. A further improvement was obtained by administering the 6-hr system twice a day. It is clear that the dosage form index decreases with more frequent dosing.

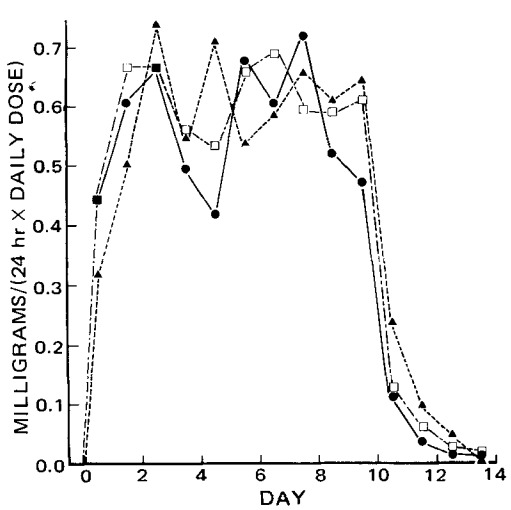

Figure 5—*Average fraction of 24-hr dose of acetazolamide excreted in the urine.*

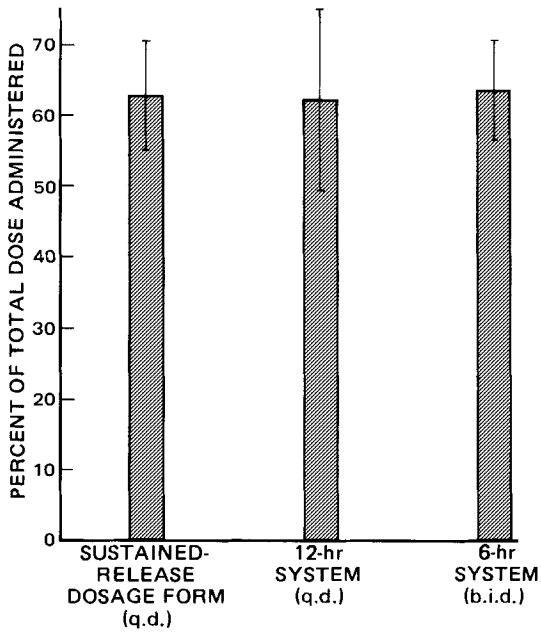

Figure 6—*Average percent of total acetazolamide dose (±SD), administered during 10 days, excreted in the urine.*

CONCLUSIONS

1. The average normalized areas under the plasma concentration–time curves are the same for the three dosage forms, about 300 (μg hr/ml)/g of daily dose.
2. The lack of significant difference in the normalized *AUC*'s indicates that all three dosage forms have essentially the same bioavailability.
3. The variability of the plasma acetazolamide concentration at the steady state is expressed as the dosage form index, DI_τ, during the dosing interval, τ, expressed in hours. The values of DI_τ, averaged within and among subjects, are: $DI_{24} = 4.9$ for the sustained-release dosage form, $DI_{24} = 3.2$ for the 12-hr system, and $DI_{12} = 1.6$ for the 6-hr system.

The 6-hr system twice a day is the only regimen with a dosage form index below 2.7, the therapeutic index for acetazolamide [Eq. 5 (4)]. This system is, therefore, expected to have a high efficacy and reduce side effects.

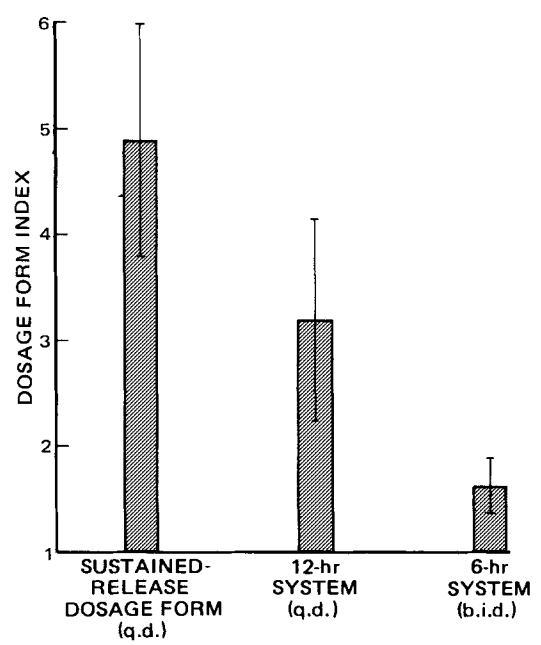

Figure 7—*Average of the maximum to minimum plasma acetazolamide concentration ratio on Days 3 and 10 (±SD).*

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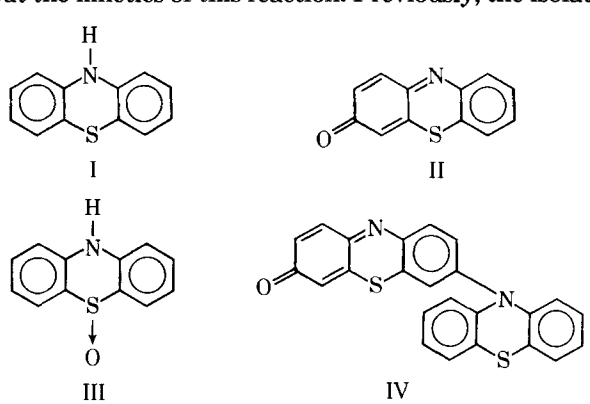
Oxidation Kinetics of Phenothiazine and 10-Methylphenothiazine in Acidic Medium

H. ROSEBOOM [x] and J. H. PERRIN [x]

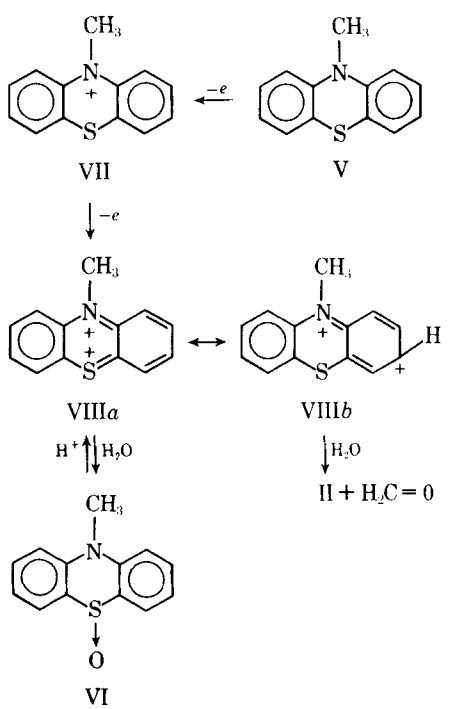
Abstract □ The rate of phenothiazine degradation in an acidic oxygen-saturated medium was studied. 3*H*-Phenothiazine-3-one and phenothiazine 5-oxide are produced by parallel reactions, and 7-(10′-phenothiazinyl)-3*H*-phenothiazine-3-one is produced in a more complex manner. The overall phenothiazine degradation rate appears to be pH independent up to pH 7.0. The degradation kinetics of 10-methylphenothiazine were studied after isolation and identification of its degradation products, 10-methylphenothiazine 5-oxide and 3*H*-phenothiazine-3-one. The main degradation product is 10-methylphenothiazine 5-oxide; but at low pH values and high temperatures, more 3*H*-phenothiazine-3-one is formed. The degradation rate of 10-methylphenothiazine is pH independent up to pH 7.

Keyphrases □ Phenothiazine and 10-methyl derivative—oxidative degradation in acidic oxygen-saturated medium, effect of pH □ Oxidation—degradation kinetics of phenothiazine and 10-methyl derivative in acidic oxygen-saturated medium, effect of pH □ Degradation kinetics—phenothiazine and 10-methyl derivative, oxidation in acidic oxygen-saturated medium, effect of pH

The oxidative degradation of phenothiazine has been the subject of many investigations (1–7), but little is known about the kinetics of this reaction. Previously, the isolation of some degradation products and their identification by TLC, melting point, and IR, UV, and mass spectral data were described (8). 7-(10′-Phenothiazinyl)-3*H*-phenothiazine-3-one was reported as a degradation product for the first time, and its structure has now been confirmed by NMR spectroscopy. The present paper reports the kinetics of the disappearance of phenothiazine (I) and the



I II III IV



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Scheme I