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DEGRADATION KINETICS OF DILTIAZEM

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ABSTRACT

The kinetics of degradation of diltiazem hydrochloride in aqueous buffered solutions (pH 1-7) were studied. Diltiazem was found to undergo hydrolysis to desacetyldiltiazem. The decomposition of diltiazem followed pseudo-first order kinetics under the experimental conditions. The drug was relatively stable over the pH range 3-6 with optimum stability at pH 5. The extrapolated shelf-life at this pH was 42.0 days compared to 15.8 day at pH 2.

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INTRODUCTION

Diltiazem hydrochloride is a potent calcium-channel blocker. It is effective when given intravenously in terminating acute episodes of paroxysmal supraventricular tachycardia (PSVT).[1,2] It is also effective when given orally in the form of sustained release tablets in preventing recurrences of PSVT.[3] Furthermore, when given in the form of aqueous solution, diltiazem is potentially useful in terminating acute attacks of PSVT.[4]

A survey of the literature showed that there has been only one study which was concerned with the stability of 1.[5] Therefore, it was decided to carry this study to elucidate the kinetics of degradation of diltiazem in aqueous solutions of varying pH.

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride, pharmaceutic grade was supplied by Dar AL Dawa Development and Investment Co., Na'ur, Jordan. Clonazepam was provided by Hoffman La Roche, Basle, Switzerland. Acetonitrile was HPLC grade. All other chemicals used were Analar grade. Double distilled water from an all-glass still was used in the kinetic studies.

Buffers

The buffers used were: at pH's 1,2 KC1-HC1; at pH's 3,4,5, McIlvaine buffer (citric acid-Ha_2HPO_4);

at pH's 6,7 Na_2HPO4-NaH_2PO4. A constant ionic strength of 0.2 was maintained for each buffer by adding an appropriate amount of NaCl. The solutions were freshly prepared and the pH's were measured at 25°C by a pH meter (Model HI 8417, Hanna Instruments, Italy).

Methods

Kinetic studies

Effect of temperature

About 50 mg of diltiazem, accurately weighed were transferred to each of three 50-ml volumetric flask and sufficient buffer (pH 2) was added to bring the solution up to volume. The buffer solution had been previously brought up to desired temperature. The flasks were stored in a constant temperature bath which was regulated by a thermostat (Erweka, West Germany) at 40, 50 or 60°C. 1-ml samples were taken at proper intervals and kept in a freezer until the time of analysis.

Effect of pH

About 50 mg of diltiazem, accurately weighed, were quantitatively transferred to a series of 50-ml volumetric flasks and sufficient buffer (pH 1,2,3, 4,5,6, or 7) was added to bring the solution up to volume. The buffer solutions were preequilibrated to 60°C. The flasks were placed in a thermostatted bath set at 60°C. 1-ml samples were drawn and stored in a freezer until the time of analysis.

Assay procedure

A stability-indicating HPLC method for the determination of 1 was used.[6] The method is based on elut-

ing solutions of diltiazem and the internal standard (clonazepam) from a MicroPak MCH-5 reversed-phase column via an injector (Model 7125 Rheodyne, USA) with a 50-ul loop size. The mobile phase consisting of acetonitrile-water (48:52% v/v) at pH 3 and 0.01 M sodium n-octane sulfonate as an ion pairing substance was delivered at a rate of 1 ml. min^{-1} (Model 2010, Varian, USA). The effluent was monitored at 239 nm using a variable wavelength detector (Model 2050, Varian, USA). Quantitation was achieved by measuring the peak height ratio of diltiazem to the internal standard.

Solutions of diltiazem and the internal standard were prepared as follows: 10 ul of the withdrawn solutions were diluted with acetonitrile to 1 ml and mixed on a vortex mixer (Model 1291, Lab-Line Instruments, USA) for 10 seconds. 50 ul of this solution were mixed with 20 ul of the internal standard (10 ng. ul^{-1}) and completed to 100 ul with acetonitrile. After mixing for 10 seconds 40 ul of the solution were injected.

RESULTS AND DISCUSSION

The influence of temperature on the degradation of diltiazem in hydrochloric acid of pH 2 is illustrated in Fig. 1. It is obvious that the degradation followed pseudo-first-order kinetics at the three temperatures. From the slopes of the straight lines it was possible to calculate the apparent first-order

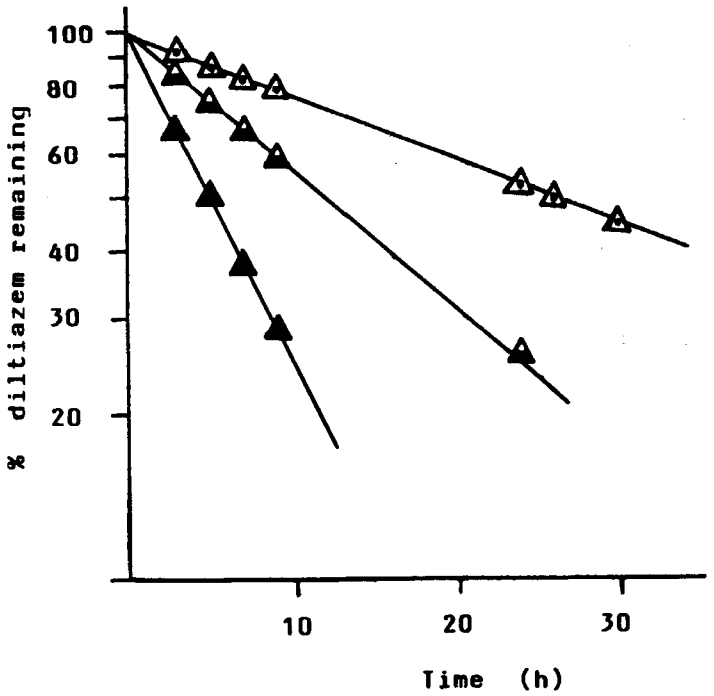


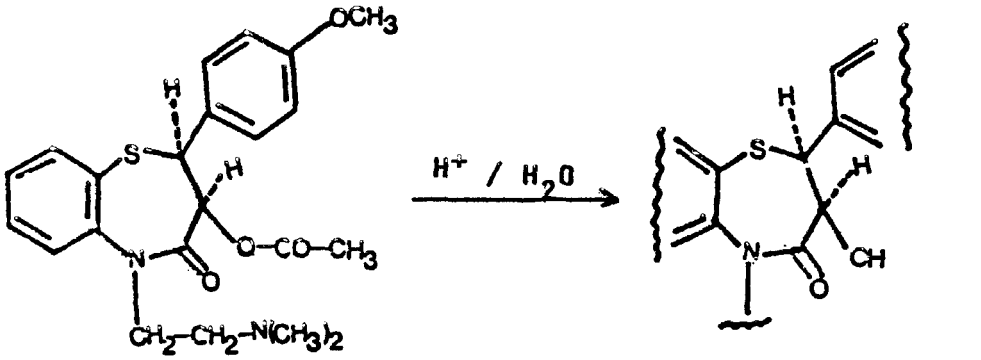
FIGURE 1

First-order plots for the hydrolysis of diltiazem in HCl-KCl buffer (pH = 2, u = 0.2) at three temperatures: △ 40°C; ▲ , 50°C; ▲ , 60°C.

rate constant (K_{obs}) and to develop an Arrhenius equation, using least square linear regression, as shown in Eqn. 1:

$$\ln K_{obs} = 23.57 - 8523.15 / T \quad (r = -0.9978) \quad (1)$$

where T is the temperature in degrees Kelvin. An activation energy (Ea) of 70.86 $kJ.mol^{-1}$ was obtained from this equation. A similar value was reported elsewhere.[5] The value of Ea may correspond to ester hydrolysis catalyzed by hydrogen ions according to the following scheme:



Diltiazem **Desacetyldiltiazem**

Desacetyldiltiazem was found to exhibit about 40 to 50% of the vasodilating potency and about 30% of the hypotensive potency of diltiazem.[7,8] The hydrolysis of the amide linkage in the 7-membered ring was not considered because the chromatogram of diltiazem showed only one peak which was assumed to be due to the hydrolysis of the ester group which is generally more labile than the amide group.

The influence of pH on the hydrolysis of diltiazem at 60°C is presented in Fig. 2. The hydrolysis in all aqueous buffer solutions followed pseudo-first-order kinetics. The rate-pH profile obtained by plotting the K_{obs} calculated from the slopes of the straight lines in the former figure against pH is depicted in Fig. 3. It is clearly demonstrated that diltiazem was most stable at pH 5 with a K_{obs} of $2.09 \times 10^{-3} h^{-1}$ at 60°C. Meanwhile, the profile shows that diltiazem is fairly stable over the pH range 3-6 with K_{obs} ranging from 2.10×10^{-3} to 3.40×10^{-3} h^{-1} at 60°C. If the Ea (70.86 KJ. mol^{-1}) was assumed to be constant over the pH range investigated,[5] a value of 1.41×10^{-4} h^{-1} may be calculated for K_{obs} at 25°C and pH 5

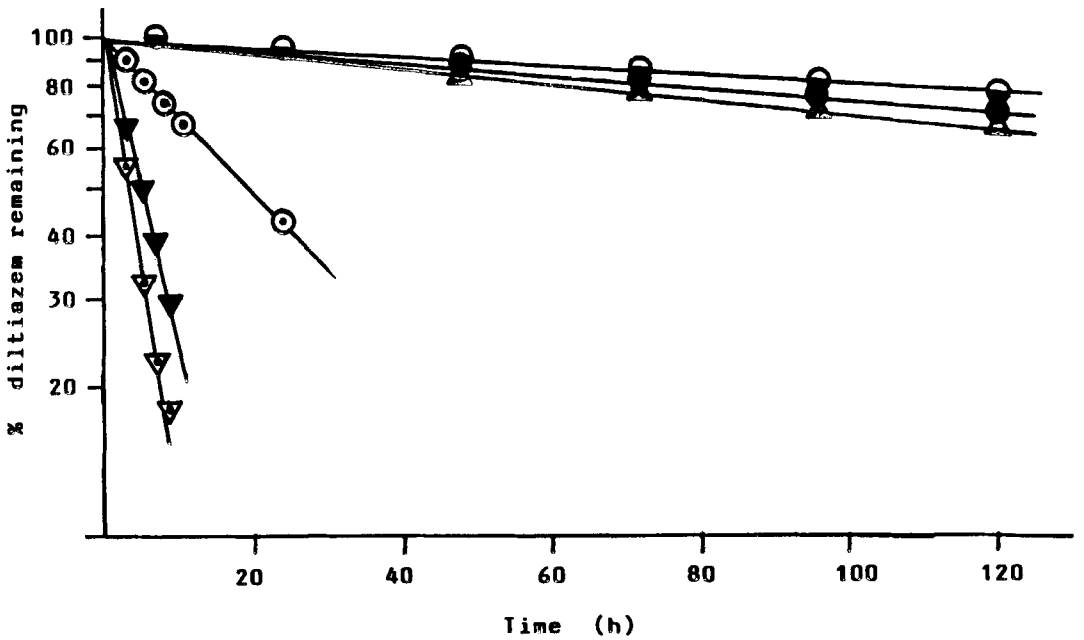


FIGURE 2

First-order plots for the hydrolysis of diltiazem at 60°C and varying pH. ▽, pH 1; ▲, pH 2; △, pH 3; ◒ pH's 4 and 6; ●, pH 5; ⊙ pH 7;

which corresponds to a shelf-life of 42.0 days. However, in another study,[5] it was reported that the pH of optimum stability of diltiazem was 4. The discrepancy between the results may be attributed to experimental design. The K_{obs} values corresponding to pH 3 and 5 were lacking in the other study[5] and hence the rate - pH profile was obtained by joining the data points at pH 2, 4 and 6.

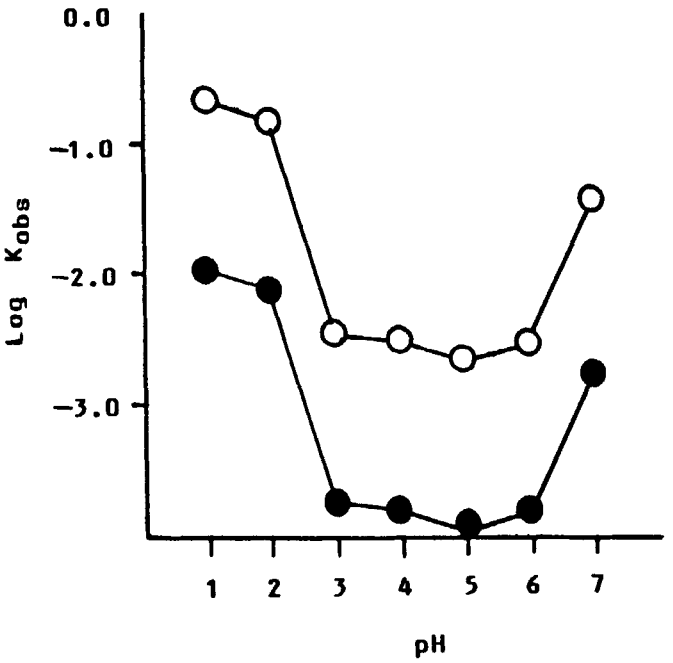


FIGURE 3

Rate-pH profile for diltiazem. ○ , 60°C; ● , 25°C predicted from accelerated stability studies at 60°C.

The kinetic behaiour of diltiazem over the entire pH range studies can be described by Eqn 2.

$$K_{obs} = K_o + K_H (H^+) + K_{OH} (OH^-) \quad (2)$$

where K_o is the first-order rate constant for the uncatalyzed hydrolysis and K_H and K_{OH} are the specific acid - and specific base-catalyzed hydrolysis, respectively. At pH values below 3, K_{obs} values were not found to be directly proportional to the hydrogen ion concentration and thus the kinetic data can be expressed by Eqn.3.

$$K_{obs} = K_H (H^+) + K_o \quad (3)$$

At 60°C and ionic strength (u) = 0.2, K_H was calculated to be 1.94 and 13.54 h^{-1} at pH's 1 and 2, respectively based on a K_o value of 2.62 x 10 h^{-1} for the pH-independent hydrolysis. Using the assumption of constant Ea with change in pH, a value of 1.17 h^{-1} was calculated for k_H at pH 2 and 25°C. Substituting the values of K_o and K_{obs} at pH 7 in Eqn. 2 and neglecting the term $K_H (H^+)$, the K_{OH} was estimated to be 3.29 x 10^5 h^{-1} at 60°C.

Briefly, it can be stated that diltiazem hydrochloride is rapidly hydrolyzed in aqueous buffered solutions into desacetyl diltiazem. Even at its pH of optimum stability (pH 5) diltiazem has an extrapolated shelf-life of only 42.0 days. Research is in progress to stabilize diltiazem in aqueous solutions using cosolvents and surfactants.

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