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## Effect of ultraviolet radiation on the stability of diltiazem

M.S. Suleiman<sup>1</sup>, M.E. Abdulhameed<sup>1</sup>, N.M. Najib<sup>1</sup> and H.Y. Muti<sup>2</sup>

<sup>1</sup> Faculty of Pharmacy, Jordan University of Science and Technology, Irbid (Jordan)  
and <sup>2</sup> Dar Al Dawa Development and Investment Co., Ltd., Na'ur (Jordan)

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Diltiazem is a calcium antagonist that has been widely used in the treatment of various cardiovascular disorders for several years (Echizen and Eichelbaum, 1986). It is used for this purpose in the form of sustained-release tablets. It has also been formulated in the form of conventional tablets and injections for the treatment of Raynaud's disease. During recent years its pharmacokinetic properties and metabolism have been studied in more detail (Rovei et al., 1980; Hermann et al., 1983; Sugihara et al., 1984). However, a survey of the literature revealed that there have been very few studies which are concerned with the stability of diltiazem (Davis et al., 1986). Such studies will be particularly useful for the formulation of diltiazem in various dosage forms. Therefore the objective of this study was to investigate the effect of ultraviolet (UV) radiation on the kinetics of degradation of diltiazem in both the solution and solid states under accelerated conditions of temperature and humidity.

Solutions of diltiazem of 1 mg/ml were prepared in KCl–HCl buffer (pH 2) or Na<sub>2</sub>HPO<sub>4</sub>–NaH<sub>2</sub>PO<sub>4</sub> buffer (pH 7) and incubated at 40°C

either in the dark or under UV radiation. Samples of 1 ml were withdrawn at appropriate intervals and stored in a freezer awaiting analysis.

Samples of diltiazem powder were incubated at room temperature at either 30% or 79% relative humidity (RH). Other samples were incubated at 40°C either in the dark or under UV radiation. In both cases aliquots of 20 mg were taken at appropriate intervals and stored in a freezer awaiting analysis. The aliquots were examined macroscopically and microscopically using a hot-stage microscope and were analyzed chemically.

Chemical analysis was carried out using a stability-indicating high-performance liquid chromatographic (HPLC) method for diltiazem (Abdelhameed et al., 1988). Chromatographic separations were carried on a MicroPak MCH-5 reversed-phase column using a Varian HPLC system. The mobile phase comprised of a mixture of acetonitrile (48%) and water (52%) and contained 0.01 M sodium *n*-octanesulfonate. Diltiazem and clonazepam (internal standard) were monitored at a wavelength of 239 nm using a variable wavelength UV detector. Quantitation was achieved by measuring the peak height ratio of drug to internal standard.

The decomposition of diltiazem in aqueous buffers of pH 2 and 7 stored in the dark at 40°C is demonstrated in Fig. 1. The linear plots of

*Correspondence:* M.S. Suleiman, Department of Pharmaceutical Technology, Faculty of Pharmacy, Jordan University of Science and Technology, Irbid, Jordan.

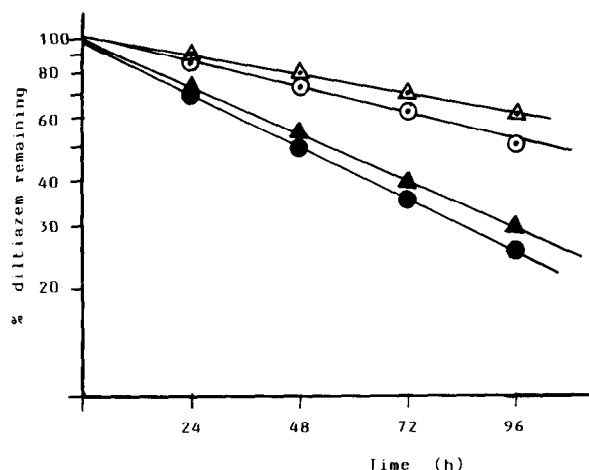


Fig. 1. First-order plots for the hydrolysis of diltiazem at 40°C. In the dark: ○, pH 2; △, pH 7; and under UV light: ●, pH 2; ▲, pH 7.

percent diltiazem remaining versus time indicate that the degradation followed pseudo-first-order kinetics. Diltiazem was hydrolyzed to desacetyldiltiazem. Similar findings were reported in another study (Davis et al., 1986).

The observed rate constants ( $k_{\text{obs}}$ ) calculated from the slopes of the plots are exhibited in Table 1. It was observed that these values were much lower than the corresponding values obtained under similar conditions except that the solutions were not protected from normal light (Suleiman et al., 1988). This indicates that even daylight may have a deleterious effect on the hydrolysis of diltiazem in aqueous solutions of varying pH.

The degradation of diltiazem in the same buffers under the same conditions except for storage under UV light is shown in Fig. 1. It is obvious that the kinetic behaviour of diltiazem decomposition under UV radiation is similar to that in the dark. The  $k_{\text{obs}}$  values obtained from the slopes of these plots are shown in Table 1. Comparison of these

TABLE 1

Rate constants for the hydrolysis of diltiazem at 40°C

pH	$k_{\text{obs}} (\text{h}^{-1}) \times 10^3$	
	Dark	UV light
2	5.20	7.04
7	1.27	1.42

values with the corresponding values obtained in the dark shows that UV radiation had a catalytic effect on the decomposition of diltiazem. However, the effect was more pronounced at pH 2 than at pH 7.

In the solid state, diltiazem was found to be highly stable. Storage of diltiazem powder at two relative humidities of 33% and 79% at room temperature for 57 days did not have any deleterious effect on its physical and chemical properties. Diltiazem did not exhibit any changes in colour, crystal shape, or melting point as indicated by hot-stage microscopic examination. Thermogravimetric studies revealed that diltiazem did not adsorb any moisture at the two RH. Further, differential scanning calorimetric studies did not show any signs of degradation as inferred by the absence of peaks other than one peak corresponding to the melting of diltiazem.

Storage of diltiazem at 40°C and a RH of 75% in the dark for 3 weeks did not affect its stability. Moreover, storage of diltiazem under the same conditions except for exposure to UV light did not affect its chemical stability and only slightly affected its physical stability. This was manifested by only a slight yellowish change in its colour.

In conclusion exposure of diltiazem aqueous buffered solutions of pH 2 and 7 to UV radiation had a deleterious effect on its stability. However, exposure of diltiazem powder to UV radiation had only a slight effect on its physical stability and no effect on its chemical stability.

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