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Studies on the photochemical decomposition of metronidazole

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Summary

The photodecomposition kinetics of the antiprotozoal drug, metronidazole, in different solvents and at different pH values, temperatures and drug concentrations has been investigated using sunlight and a photochemical reactor. The drug in the presence of its decomposition products was analyzed using different chromatographic and spectroscopic techniques. The photodecomposition of the drug was found to follow pseudo-first-order kinetics.

Metronidazole is widely used in the Sudan for treatment of amoebiasis, trichomoniasis and giardiasis (Gordeeva, 1965). Like other drugs containing imidazole rings, e.g. midazolam (Selkamaa and Tammilehto, 1988), metronidazole has been reported to be sensitive to light (Willkin and Moore, 1988). A few reports on the photostability of metronidazole have recently been published (Habib and Asker, 1989; Ebel et al., 1990).

The strong sunlight and subtropical conditions which prevail in the Sudan have made investigation of the photodecomposition of metronidazole, under such conditions, of prime concern. Such a study would require establishment of a reliable method of analysis of metronidazole simultaneously with its possible decomposition products.

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The photodecomposition kinetics of metronidazole in different solvents (water, methanol, isopropanol and chloroform) was studied using sunlight and a photochemical reactor. The sunlight-degraded and UV-irradiated samples of metronidazole solution were analyzed using thin-layer chromatography (TLC), gas-liquid chromatography (GLC), UV and fluorescence spectroscopy.

The UV- and sunlight-degraded samples of metronidazole were investigated by TLC using silica gel as an adsorbant and benzene : methanol : diethylamine (5 : 1 : 1) as a solvent system. The results revealed the presence of two fluorescent spots on TLC (R_f 0.5, blue; R_f 0.15, yellow) when visualized under UV light. Metronidazole itself appeared as a dark non-fluorescent spot (R_f 0.86). On further development of the plate, this spot separated into two, indicating the presence of a third non-fluorescent decomposition product of a possibly close structural similarity and chromatographic behavior to metronidazole.

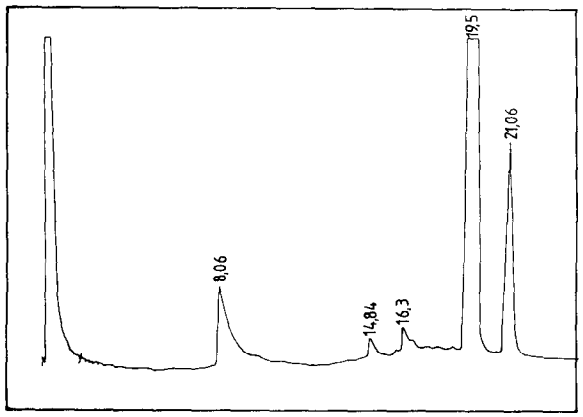

Fig. 1. GLC chromatogram of an aqueous solution of metronidazole exposed to sunlight for 3 weeks. Peaks with the retention times of 8.06 and 21.06 min are due to the main decomposition products; the peak with the retention time of 19.5 min is due to metronidazole.

Direct analysis of the decomposed sample of metronidazole solution by GLC using an OV-17 column at a temperature of 200 °C showed the presence of one peak corresponding to metronidazole. On methylation with hydrochloric acid and methanol, no further peaks appeared on the chromatogram. However, on acetylation with acetic anhydride in pyridine, a number of peaks appeared. These peaks were found to be well separated when using temperature programming (between 110 and 200 °C at a rate of 10 °C/min; Fig. 1). The peaks that appeared at 8.06 and 21.06 min represent the major decomposition products. The identities of the peaks remain unknown.

The UV spectrum of metronidazole in water revealed the presence of three absorption bands

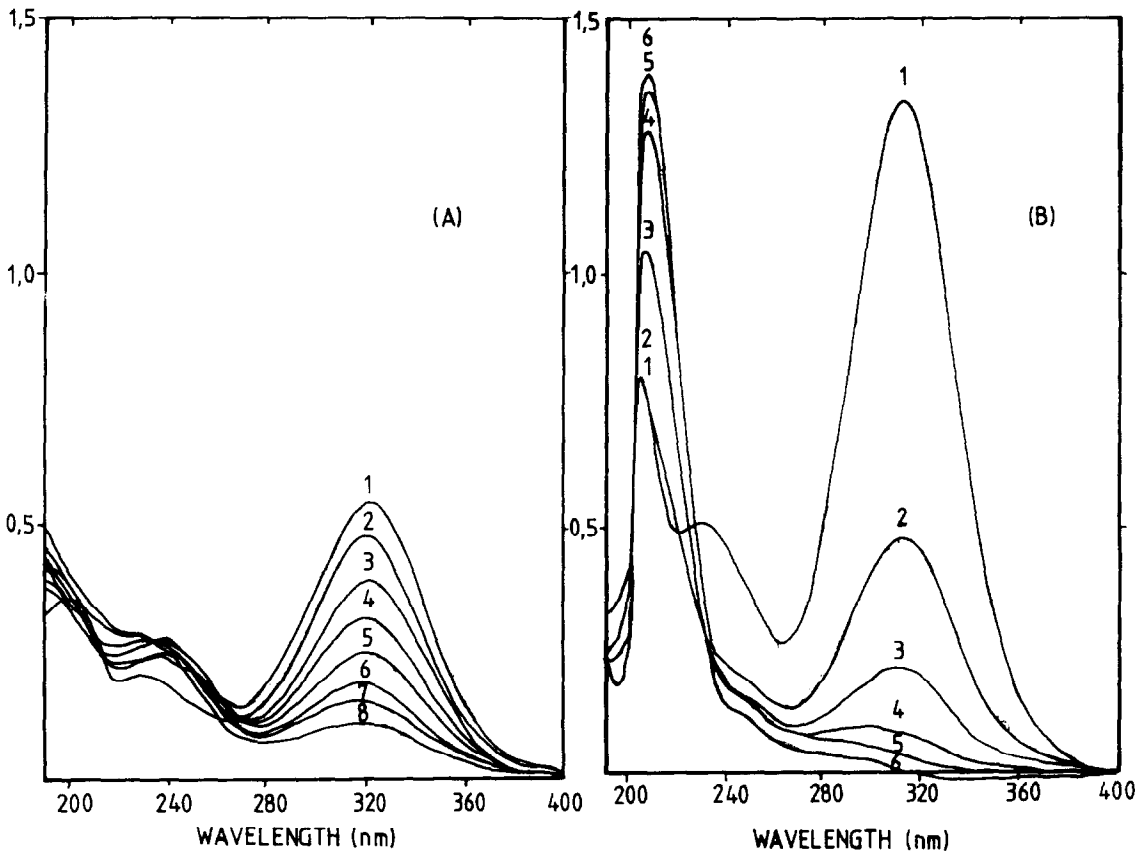

Fig. 2. UV spectra of metronidazole solutions: (A) in water and (B) in methanol recorded at 30 min intervals of irradiation (designated 1–8).

at 201, 230 and 320 nm (λ_{max}). The intensities of the bands decreased with time of irradiation, however, the appearance of new bands in the spectrum was not observed (Fig. 2A). The UV spectra of solutions of metronidazole in organic solvents, e.g. methanol and *n*-propanol, demonstrated the presence of three bands at 200, 230 and 310 nm (λ_{max}). however, on irradiation of these non-aqueous solutions, the intensities of the bands at 230 and 310 nm decreased while that at 200 nm increased with time of irradiation (Fig. 2B).

Solutions of metronidazole in water and in methanol do not show any fluorescence. However, on irradiation of both solutions, fluorescence peaks appear (λ_{Ex} 281 nm, and λ_{Em} 312 nm). The weak fluorescence obtained was found to increase with time of irradiation. Irradiated aqueous solutions of metronidazole showed greater fluorescence compared to the corresponding methanolic solutions.

The photodecomposition of metronidazole was found to depend on the following factors: solvent, pH, temperature and light source. The rate of decomposition in water, methanol, isopropanol and chloroform was determined to be 0.21, 0.32, 1.02 and 1.6 h^{-1}, respectively. This implies that the rate of decomposition increases with decreasing solvent polarity and when using a solvent that readily forms radicals. This result suggests that a radical formed by the solvent could be involved in the decomposition process.

The photodecomposition reaction of the drug appears to follow pseudo-first-order kinetics. The rate of decomposition was found to increase with temperature, pH and intensity of radiation and to decrease with increase in drug concentration. The presence or absence of oxygen was found to exert very little effect on the photodecomposition rate of metronidazole. This may be taken as an indication that oxidation or reduction reactions might not participate in the decomposition process of the drug.

From this study, it can be concluded that metronidazole is a photolabile drug and should be protected from direct sunlight especially in infusion forms where the concentration (5 mg/ml) is relatively low compared to that in suspension forms (40 mg/ml). Water, in which the photostability is high, is the best vehicle for the preparation of the drug.

UV spectroscopic techniques of analysis are not the methods of choice for detection of the photodecomposition products of metronidazole. However UV is quite useful for the determination of the drug and for studying the kinetics of its decomposition. This is because of the findings that none of the UV bands of the decomposition products interfere with that used for the determination of the drug. HPLC with UV detection (commonly used detector) can be used for the determination of metronidazole. However, some difficulties will be encountered in attempting to detect the photodecomposition products, since they all absorb at a very short wavelengths. On the other hand, the more polar decomposition products have been reported to become irreversibly adsorbed to the column (Ebel et al., 1990). This is an additional drawback to the difficulties that are met in employing HPLC to analyse the metronidazole decomposition products.

On the basis of the present data, TLC and GLC techniques in which metronidazole and its decomposition products can be detected simultaneously are strongly recommended for stability testing, detection and analysis of degraded samples of the drug.

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