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Studies on the thermal and photochemical decomposition of mebendazole

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Abstract

TLC analysis of sun- and UV-decomposed samples of mebendazole solutions revealed the presence of three spots under UV light. These were found to be due to the unchanged drug M ($Rf = 0.33$) and two decomposition products I ($Rf = 0.58$) and II ($Rf = 0.82$).

The major decomposition product I ($Rf = 0.58$) was isolated, purified and analyzed using different analytical techniques. The kinetic studies showed that the photo-decomposition of mebendazole appeared to follow first-order reaction kinetics. The rate of photo-decomposition was dependent on intensity of radiation, concentration of the drug, pH, solvent and additive.

Keywords: Mebendazole; Photo-decomposition; Thermal-decomposition; Stability; Kinetics

1. Introduction

Human infection caused by helminth (worms) is a significant medical problem, especially in developing countries in tropical climates. Different agents have been used for treatment of such infection. The most common one is mebendazole. Mebendazole, a benzimidazole carbamate derivative, is an anthelmintic drug used principally for the treatment of intestinal nematode infection (Muttalib et al., 1981; Wahlgren and Frolov, 1983; Shield, 1984; Abadi, 1985). Like other light sensitive drugs containing imidazole ring, e.g. Midazolam (Selkamaa and Tammilehto, 1989) and Metronidazole (Willkin and Moore, 1988; Habib and Asker, 1989; Ebel et al., 1990; Karim et al., 1991), mebendazole is expected to be sensitive to light.

The strong sunlight and subtropical conditions which prevail in the Sudan have made investigation of thermal- and photo-decomposition of mebendazole, under such conditions, a primary concern. The photo-decomposition kinetics of

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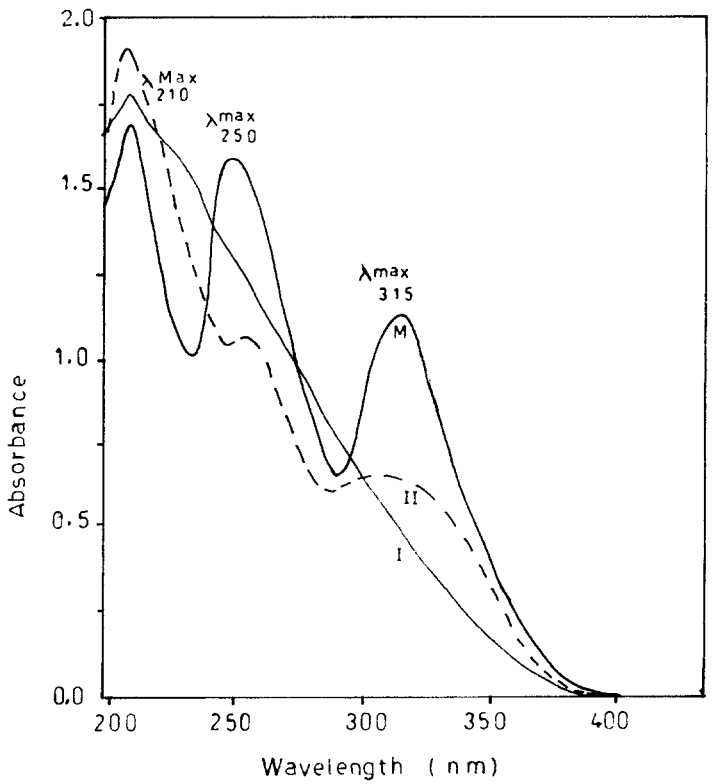

Fig. 1. UV Spectra of mebendazole (M) and the photo-decomposition products I and II.

mebendazole at different conditions and in the presence of different additives was studied using sunlight and UV. Sunlight- and UV-degraded samples of mebendazole solutions were analyzed using thin layer chromatography (TLC), UV and fluorescence spectroscopy.

2. Materials and methods

Thin layer chromatography was carried out on silica gel GF254 plates using chloroform:methanol:diethylamine (85:10:5) as a solvent. For photodegraded sample the developed plates, when visualised under UV, revealed the presence of two fluorescent spots ($Rf = 0.58$ and 0.82) for decomposition products I and II respectively. The undecomposed mebendazole, M, appeared as a third fluorescent spot at $Rf = 0.33$. Only two spots were obtained when a thermally-decomposed sample of mebendazole solution was analyzed. These corresponded to undecomposed mebendazole M ($Rf = 0.33$) and the decomposition product I ($Rf = 0.58$).

3. Results and discussion

The pattern of photo-decomposition of mebendazole in solution and solid form was found to be the same. However, the rate of photo-decomposition of mebendazole in solution was greater than that in solid form. The photo-decomposition products I and II were isolated and purified using preparative TLC and recrystallization from methanol and acetone.

The major photo-decomposition product I ($Rf = 0.58$), which was obtained on thermal- and photo-decomposition, consisted of yellowish needle-shaped crystals that melted at 158°C. This

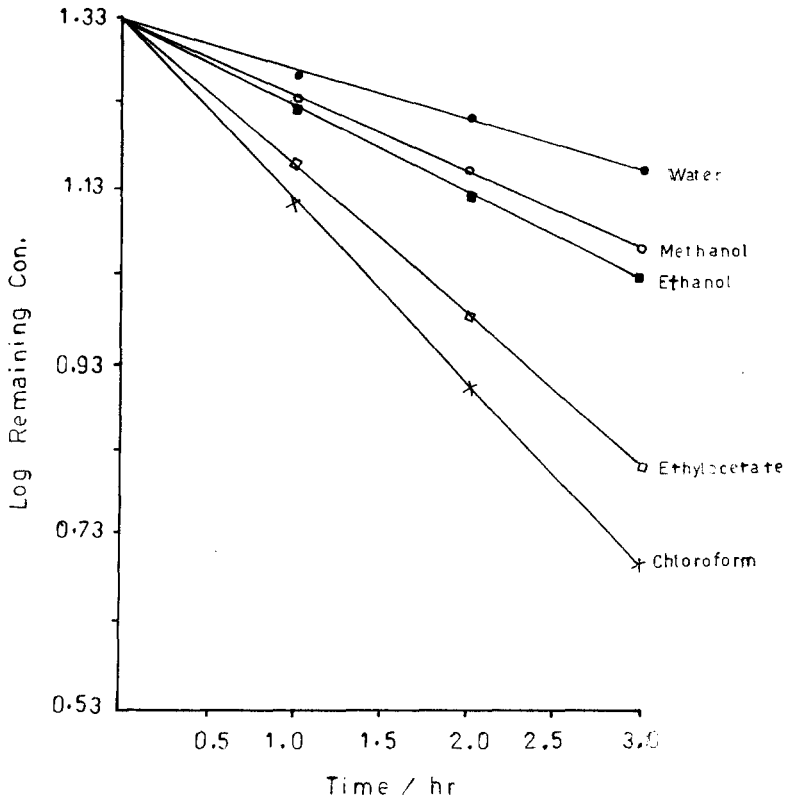

Fig. 2. Effect of solvent on mebendazole photo-decomposition.

product was practically insoluble in chloroform, acetone ethyl acetate, water and ether; it was soluble in methanol, dimethyl sulphoxide and in concentrated and diluted mineral acids.

UV spectrophotometric analysis of mebendazole showed that the spectrum consisted of three absorption bands (Fig. 1) at λ_{max} values of 210, 250 and 315 nm. However, the UV spectrum of the photo-decomposition products I and II showed the presence of only one band at 210 nm. This indicated that the principal chromophore responsible for the absorption at λ values of 250 and 315 nm in mebendazole was destroyed on irradiation. The disappearance of these two absorption bands was also observed on recording the UV spectrum of mebendazole solution after different periods of irradiation. Therefore, these two absorption bands were chosen for selective analysis of mebendazole in the presence of their decomposition products and for the study of its photo-decomposition kinetics.

Table 1
Photo-decomposition rates of mebendazole solutions containing certain concentrations of different additives

Additive	Concentration (%)	Reaction rate K (h^{-1})
CMC	0.1	0.091
Sodium CMC	0.1	0.127
PVP	0.1	0.170
Sodium benzaote	0.1	0.22
Sodium saccharine	0.2	0.29
Keltron	0.1	0.45
Glycerol	1	0.58

Fluorescence studies showed that both mebendazole and its photo-decomposition products gave a very weak fluorescence at a λ_{max} excitation value of 390 nm and a λ_{max} emission value of 506 nm.

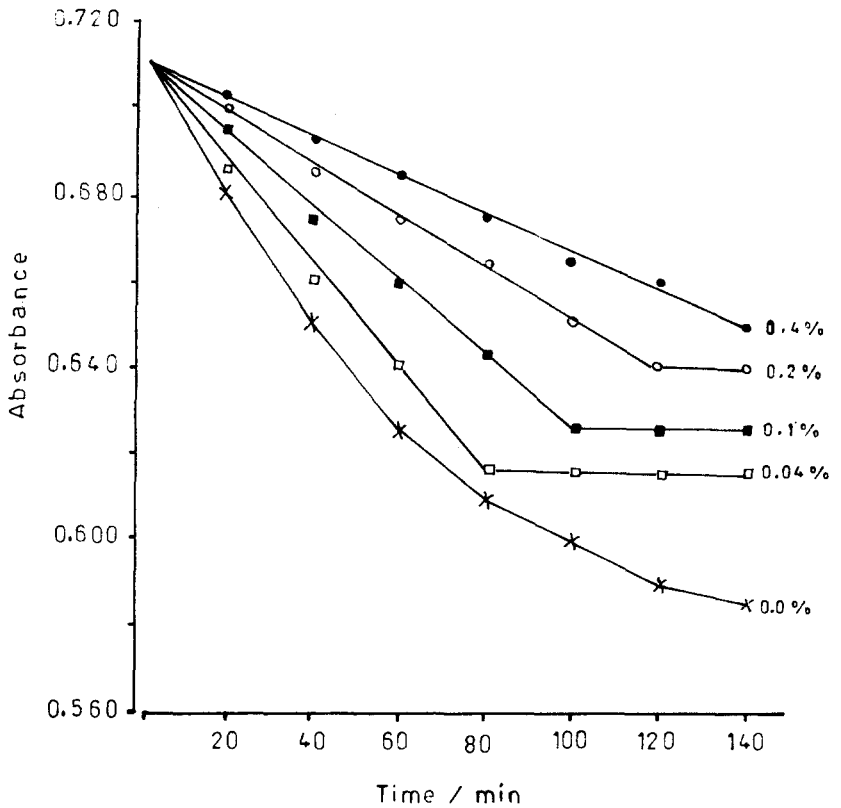

Fig. 3. Effect of sodium benzoate concentration on mebendazole photo-decomposition.

The kinetic studies showed that the photo-decomposition appeared to follow a first-order reaction kinetics and the rate of photo-decomposition was found to be dependent on temperature, pH, intensity of radiation, solvent and drug concentration. The drug was found to be very stable to photo-decomposition at acidic pH. However, at pH greater than 6 the drug started to decompose rapidly on irradiation.

The rate of photodecomposition was found to increase on decreasing the polarity of solvent and on using solvents that readily form radicals on irradiation (Fig. 2). This result suggested that radicals formed by the solvent could easily be involved in the decomposition process.

A rational way to develop approaches which will increase the stability of rapidly degraded drugs in pharmaceutical dosage forms is through thorough study of factors which affect such stability. Among these factors is the presence of additives which are commonly used in pharmaceuticals. Therefore, the effect of these additives, within the concentrations range usually used, on the photo-decomposition of mebendazole was studied. Among the additives studied were sucrose, sodium carboxylmethyl cellulose (NaCMC), carboxymethyl cellulose (CMC), povidone (PVP), sodium benzoate, sodium saccharin, keltron and glycerol. The presence of any of these additives was found to decrease the rate of photodecomposition of mebendazole and this decrease was found to be dependent on concentration. The most effective additive in stabilization of mebendazole was found to be CMC (Table 1). The reaction rate was observed to be changed from first-order reaction kinetics to zero-order reaction kinetics on using sodium salts of CMC, benzoic acid and saccharin. Moreover, in the presence of sodium benzoate it was observed that the photo-decomposition of mebendazole gradu-

ally increased with time of irradiation until a time was reached where no further decomposition was observed (became stable). This time was dependent on sodium benzoate concentration, increasing with an increase of sodium benzoate (Fig. 3). This result could be explained in terms of micelle formation (Cooper and Gunn, 1972), complex formation or some type of association between sodium benzoate molecules and the mebendazole molecule which was time and concentration dependent.

4. Conclusions

From this study it can be concluded that mebendazole is a thermal and photo-sensitive drug, its stability can be affected by heat and exposure to light. The extent of photo-decomposition is greater in solution and is higher than thermal decomposition.

The kinetics of photo-decomposition was found to be first-order. This order of reaction was found to be altered by the presence of some additives, e.g. sodium benzoate.

The photo-decomposition was found to be dependent on temperature, pH, concentration, intensity of radiation, solvent and additive. The photo-decomposition of mebendazole decreased in the presence of these additives. Among the additives studied, the most effective one in decreasing the rate of photo-decomposition was found to be CMC.

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