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COMPARATIVE PHOTOSTABILITY STUDY OF FANCIMEF TABLET AND IT'S ACTIVE INGREDIENTS

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Fancimef tablet is one of the multi-component drugs recently introduced into malaria therapy to combat the resistant strains of Plasmodium parasite. Like most complex organic compounds, it is expected that the organic compounds in Fancimef tablet will absorb light spectra leading to its photodecomposition and all its attendant problems. In this study, a comparative photostability study of the Fancimef tablet and its active components was undertaken. The results obtained showed that the active ingredients of Fancimef tablet undergo photodecomposition in buffer solutions while the dry Fancimef tablet (powder) is photostable. Thus suggesting that Fancimef tablet is not susceptible to photodecomposition.

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INTRODUCTION

Fancimef tablet (FT) is one of the latest multi-component drugs introduced into malaria therapy due to its high activity against strains of Plasmodium. Each FT contains as its active ingredients Mefloquine, HCl, Sulfadoxine, and Pyrimethamine in the ratio 10:20:1. Reid (1968) defined drugs as complex organic molecules capable of absorbing light leading to their photodecomposition and photodegradation.

Some of these photodegradation and photodecomposition products have been found to be capable of inducing photosensitizing response in-patients, thus leading to photosensitivity-induced dermatological problems. Furthermore, the process of degradation in some cases has resulted in biologically inactive or harmful products (Chignell *et al.*, 1980).

Tonnesen (1991) submitted that photochemical reactions could occur directly on drug in pure soluent or sensitized on drugs in formulations. Thus many drugs have been reported to undergo photodegradation and decomposition on expossure to light. Thiazide diuretics (Tamal *et al.*, 1983; Vagi *et al.*, 1991), tetracycline (Moore *et al.*, 1983), chloramphenicol (Reish *et al.*, 1983), amodiaquine and chloroquine (Owoyale, 1989; Greehill *et al.*, 1990) are a few examples of such drugs.

This study was undertaken to investigate the photostability of dried Fancimef tablet (powder) and its active ingredients. The results of this study showed that although the Fancimef tablet in buffer solutions was photolabile since it has been disintegrated to its components, the dry Fancimef tablet did not undergo photodecomposition easily.

MATERIALS AND METHODS

Drugs and Chemicals

Roche Pharmaceutical Company Lagos Nigeria donated FT and pure reference powders of Sulfadoxine, Pyrimethamine and Mefloquine Hydrochloride. Dichloromethane and Methanol (HPLC grade) were supplied by B.D.H.

Method:

(i) Separation of the active ingredients of FT was by the preparative TLC separation method as reported by Clarke 1986.
(ii) Preparation of sample for exposure to sun light.

(a) Twenty clean-dry test tubes were divided into A, B, C, & D sets, each set containing five test tubes. 50mg of dried powdered FT were weighed into each of the test-tube used for this experiment.

To group A tubes, 10mls of buffered solution pH = 4 were added; group B, 10mls of buffered solution pH = 10 were also added while to group C, 10mls of methanol were added. Group D set of tubes contained only 50mg dry powdered FT and served as control.

(b) 10mg each of the pure reference powders of Sulfadoxine, Mefloquine HCl and Pyrimethamine respectively were weighed into each of these 20 test tubes. The tubes were then sub-divided into groups, A, B, C and D and treated as in (IIa) above and exposed to sunlight.

(c) 10mg each of the extracted components of FT, namely Sulfadoxine, Mefloquine HCl and Pyrimethamine were also treated as in (IIa) above and exposed to sunlight.

(d) Similar tubes were prepared and processed as in (IIa, b & c) above but this time kept in dark cupboard unexposed. Spotting of the samples from the tubes were done once daily for two weeks and thereafter once weekly for six weeks. These procedures were repeated ten times and the average RF's values were recorded in Table 1.

RESULTS

After twenty-one days of investigation (Table 1) Sulfadoxine produced four decomposition products, Pyrimethamine two new products while Mefloquine HCl photodegraded to give two new products. Spectra studies of these products confirmed their structures. Figure 1 shows a comparative Rf's of the decomposition products of the ingredients of FT at different times of exposure to sun light in a solution of pH = 10.

DISCUSSION

Dry exposed FT is not photolabile While its exposed solution undergo photodecomposition, the pattern of which was unaffected by the pH of the media. Figure 1 shows the comparative Rfs' values of the photodecomposition products of the active ingredients of FT and the dry FT at different times of exposure to sunlight. At the end of the investigation, (21 days) all the active components of FT have shown increased number of Rf values, while the Rf values of the dry Fancimef tablet still remained the same. (Fig.1) showing that these active ingredients have undergone total or partial decomposition while dry Fancimef Tablet has not. Among the photodecomposition products of FT ingredients were Sulfanilamide, aniline, methyl and nitro-derivative of Sulfadoxine. These are photo-degradation products of Sulfadoxine as confirmed by absorption spectroscopy using the method of Dryer (1966). Pyrimethamine at the same time and under the same condition degraded to form two new compounds, 5-hydroxyl phenyl and N-oxide derivatives of Pyrimethamine. This observation corroborates the earlier claims of Oppenlaender *et al* (1988). The only identified product of Mefloquine HCl was 2, 8-bis (trifluoro) methyl cinchonic acid, a production which Tonesen (1990) obtained as result of photochemical decomposition of mefloquine in water. Thus, it is seen that the components of FT are photolabile, while FT itself is not easily affected by exposure to sunlight. This explains the high activity of FT against resistant strains by Plasmodium.

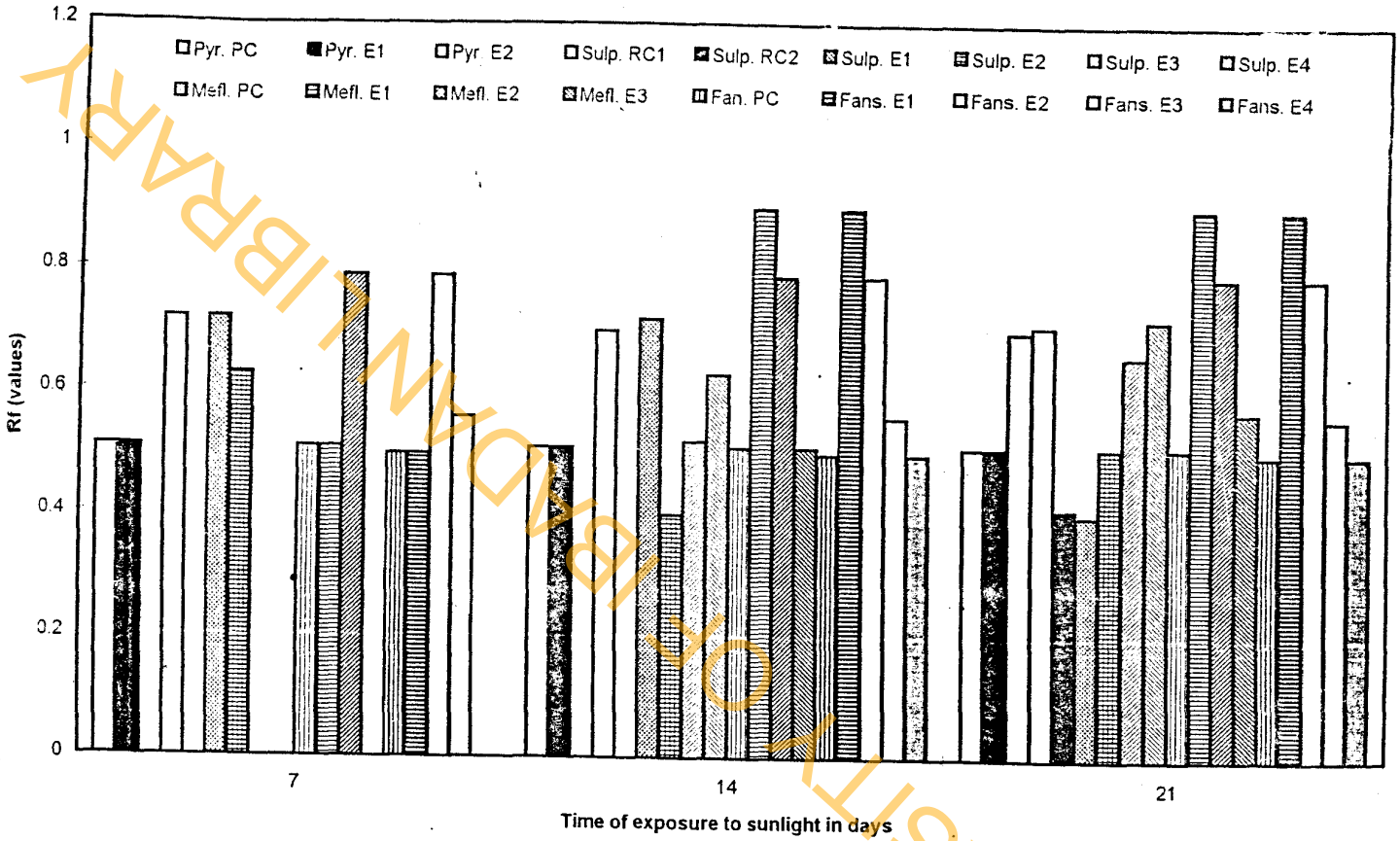

FIGURE 1

Rf values of photodecomposed products produced when extracted active ingridients of fansimef[R] are exposed to sunlight in phosphate buffer solution pH 10.0 for 7, 14 and 21 days.

CATEGORY OF DECOMPOSED COMPOUNDS

Pyr. PC – Pyrimethamine Covered Pyr. El – Pyrimethamine Exposed Decomp. Compd. 1 Pyr.E2 – Pyrimethamine Exposed Decomp. Compd. II Sulp. RC1 – Sulphadoxine Covered I Sulp. RC2 – Sulphadoxine Covered II Sulp. El – Sulphadoxine Exposed Decomp. Compd. I Sulp.E2 – Sulphadoxine Exposed Decomp. Compd. II Sulp. E3 – Sulphadoxine Exposed Decomp. Compd. III; Sulp. E4 – Sulphadoxine Exposed Decomp. Comp. IV; Mefl. PC –Mefloqune Covered; Mefl.E1 –Mefloquine Exposed Compd.I; Mefl.Es –Mefloqune Exposed Compd.II; Mefl. E3 – Mefloquine Exposed Compd. III; Fans. PC –Fansimef Covered; Fans E1 –Fansimef Exposed Compd. I; Fansimef Exposed Compd. II Fans. E3- Fansimef Exposed Compd. III.

Table 1
Rf values of the active ingredients of Fancimef Tablet in buffer solution & pH = 10.0

Category of samples		Rf values of photo degradation products in days.					Remarks
		0	3	7	14	21	
1.	Dried pure Powder Fancimef	0.51 0.61 0.72	0.51 0.61 0.72	0.51 0.61 0.72	0.51 0.61 0.72	0.51 0.61 0.72	Control covered samples No photodegradation.
2.	Extracted active ingredient dissolved in buffer soln.	0.51 0.61 0.72	0.51 0.61 0.72	0.51 0.61 0.72	0.51 0.61 0.72	0.51 0.61 0.72	Exposed Test Samples Colour change indicated the Formation of new photodegradation product which could not be separated for analysis
3.	Reference dried *Mefloquine* Power	0.61	0.61	0.61	0.61	0.61	Controls. Covered Reference sample No. Photodegradation.
4.	Extracted *MELFLOQUIN E* powder in buffer soln.	0.61	0.51	0.81 0.51	0.81 0.51	0.81 0.51	Exposed Test Sample 2,8-bis (trifluoro) methyl cinchonic acid formed the (Tonesen 1990) there are the Photodecomposition product (Tonesen 1990).
5.	DRY *SULFADOXIN E* powder	0.72	0.72	0.72	0.72	0.72	Control covered reference dry sample. No decomposition product.
6.	Extracted *Sulfadoxine* in soln.	0.72	0.72	0.72 0.63	0.40 0.72 0.63 0.52	0.40 0.52 0.63 0.72	Exposed Test sample: 4 decomposition product formed are 5-hydroxyl phenyl, methyl and N-oxide derivatives of *Sulfadoxine*, aniline, Sulphanilamide-(Greenhill 1990)
7.	Dry sample *Pyrimethamine* powder	0.61	0.61	0.61	0.61	0.61	Covered control sample Dry, no decomposition
8.	Extracted *Pyrimethamine* in soln.	0.61	0.61	0.61	0.61 0.66	0.61 0.66 0.63	Exposed test sample. 2 photodecomposition products formed are: 5-hydroxyl phenyl and M-oxide derivative of *Pyrimethamine* (Oppenlaender *et al* 1988)

N.B: All samples were prepared on silica gel GL254. Mobile phase was dichloromethane: Methanol (9:1). Solvent chloroform. Coefficient of Variation: Pyrimethamine 1.2% (STD = 1.1%) ; Mefloquine 1.6% (STD = 1.6%) Sulphadoxine .8%.

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