POLYENE MACROLIDE DERIVATIVES. II

PHYSICAL-CHEMICAL PROPERTIES OF POLYENE MACROLIDE ESTERS AND THEIR WATER SOLUBLE SALTS

Sir:

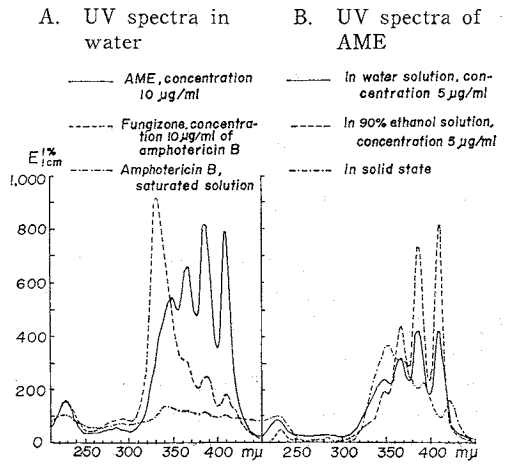
Previously[1], we reported that the methyl ester of amphotericin B retained the full antifungal activity of the parent antibiotic. Since amphotericin B exists as a zwitterion, the methyl ester derivative is basic, and it was then conceivable that upon treatment with acids a water-soluble salt could be obtained. Amphotericin B methyl ester hydrochloride (AME) was prepared and exhibited full activity and excellent solubility in water. Other polyene antibiotics, known to exist as zwitterions, were also converted into the methyl ester hydrochloride derivatives, and all exhibited the full antifungal activity[2] of the parent antibiotics and a very good solubility in water. A comparison of the water-solubility of a variety of polyene macrolides and their methyl ester hydrochloride derivatives is given in Table 1.

Table 1. Solubility of polyene macrolides and their methyl ester hydrochloride derivatives in water at 25°C

Antibiotics and ester derivatives	Type of chromophore	$E^{1\%}_{1cm}$ in methanol	Solubility* mg/ml
Nystatin	Tetraene	790	0.0390
Nystatin methyl ester·HCl	Tetraene	750	>80.0000
Pimaricin	Tetraene	980	0.0520
Pimaricin methyl ester·HCl	Tetraene	900	>80.0000
Mediocidin	Hexaene	1,100	0.0720
Mediocidin methyl ester·HCl	Hexaene	1,000	>50.0000
Amphotericin B	Heptaene	1,580	0.0017
Amphotericin B methyl ester·HCl	Heptaene	1,500	>75.0000
Candicidin	Heptaene	950	0.0320
Candicidin methyl ester·HCl	Heptaene	800	>20.0000
Trichomycin	Heptaene	800	0.0460
Trichomycin methylester HCl	Heptaene	750	>20.0000

* Saturated solution was centrifuged at 10,000 r.p.m. for 20 minutes and the amount of solute measured on a dry weight basis or spectrophotometrically after dilution 1/10 with methyl sulfoxide.

Fig. 1. Ultraviolet spectra.



The remarkable solubility of the methyl ester hydrochloride derivatives in water resembles that of the N-acetyl derivative salts of the polyene antibiotics with alkaline bases[3]. However, the N-acetyl derivatives are significantly less active than the parent antibiotics and have found no chemotherapeutic application. The solubilization of polyene antibiotics in water without a decrease of activity had been achieved by complexing the antibiotics with detergent-like bile salts, that most effective being sodium desoxycholate[4]. Fungizone (E. R. Squibb & Sons, Inc.), is a commercially available complex of amphotericin B and sodium desoxycholate. It was considered important to compare AME and Fungizone. The biological evaluation is reported elsewhere[2]. A physical-chemical comparison was performed spectrophotometrically by making use of the characteristic absorption of both compounds in the ultraviolet-visible region. The spectra of AME, Fungizone and the parent amphotericin B in water are given in Fig. 1 A. AME displays a strong vibrational fine structure in contrast to the highly degraded spectra of Fungizone and amphotericin B. This reflects, in our opinion, differences between the physical states of the molecules of these compounds in water. It was sug-

gested before[4] that molecules of amphotericin B and Fungizone tend to form micelles or colloidal dispersions in water. Such association of molecules undoubtedly affects the free oscillation of electrons along the chain of the conjugated double bonds and results in the spectral degradation, most severe in the fine structure. The effect of association of molecules on the ultraviolet-visible spectrum is demonstrated in Fig. 1 B. It compares the absorption curves obtained for AME in solid state and in solutions in ethanol and water. In the solid state, which is an extreme case of association of molecules, the spectrum is degraded as expected, in contrast to the spectrum in solution. The spectrum of AME in water is partially degraded as compared with the spectrum in ethanol at the same concentrations of solute. This indicates that AME in water still exists in forms of micelles. The degree of dispersions, however, seems to be much higher than for Fungizone in water, approaching closer to molecular dispersion or true solution.

This basic difference from Fungizone in aqueous solubility and micelle formation could play an important role in determining the antifungal efficacy and toxicity of AME *in vivo*.

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