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PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS OF FURAZOLIDONE AND ITS COMPLEXATION WITH AMINO ACIDS

SANTWANA GAUR*, RAJNI PUROHIT and MAMTA RANKA

Department of Chemistry, J. N. V. University, JODHPUR – 342001 (Raj.) INDIA

ABSTRACT

Newly synthesized drug, furazolidone from the reaction of 5-nitro-2-furaldehyde and 3-amino-2-oxazolidinone with effective pharmacokinetic and pharmacodynamic parameters, interacts with amino acids viz, cysteine, histidine, tyrosine and trypotophan to form complexes. The stability of the complexes indicates fairly stable complex formation. Thermodynamic and IR spectral parameters were obtained.

Key words : Furazolidone, Thermodynamic, Spectral, Pharmacokinetic, Pharmacodynamic.

INTRODUCTION

Drug discovery is the process that leads to the introduction of a new drug into clinical therapy. Though it is not easy to design drugs, however, application of sophisticated methods of structural analysis viz. spectroscopy, chromatography etc., helps in drug designing.

In order to understand the complex physiological processes based on chemical and physical reactions taking place in an organism, drug designing is done. Thus, it is the study which makes possible the use of drugs more rationally, observe their action on an organism and control their molecular structure to obtain the desired pharmacological effect. The result of pharmacological test of the drug ascertain the possibility of using them in medical practice[1-3] and the action of the drugs is ascertained by its chemical structure as well as its physicochemical properties[4-6].

With such perceptive, one should mention about furazolidone (FZD), which is having antibacterial and antiprotozoal actions. It finds use in the treatment of diarrhoea and gastroenteritis of bacterial origin. It is also used in the treatment of giardiasis.

* Author for correspondence

Simple amino acids, which are constituents of proteins, are expected to interact with the drug molecule in aqueous solution spectrophotometrically at different temperatures. The observations are reported in the present communication.

The equilibrium constants of the complexes were determined assuming the composition of the complexes to be 1 : 1.

The equilibrium constant K for the reaction,

$$A + D \rightleftharpoons AD$$

can be written as

$$K = \frac{[AD]\,\gamma_{AD}}{[A][D]\gamma_A\gamma_D}$$

Where [A], [D] and [AD] are the equilibrium concentrations of A, D and AD respectively and γ is the activity coefficients, respectively. Here A is the amino acid and D = FZD.

In view of low concentrations of reactants and products and unchanged nature of the molecules $\gamma_{AD}/\gamma_A\gamma_D$ be reasonably regarded as unity.

Now the expression can be written as –

$$K = \frac{x}{(C_1 - x)(C_2 - x)}$$

Where x is the equilibrium concentration of the complex AD, C_1 and C_2 are the initial concentrations of A and D, respectively.

ΔG^0, the standard Gibb's energy changes were calculated from the relation –

$$\Delta G^0 = 2.303\ RT \log K$$

EXPERIMENTAL

An equimolar (25 cm^3) ethanolic solutions of 5-nitro-2-furaldehyde (0.01 M, 0.141 g) and 3-amino-2-oxazolidinone (0.01 M, 0.102 g) were mixed thoroughly and refluxed for 6 hrs in presence of o-toluene sulphonic acid. It was filtered, dried and its purity was tested

by m.p. determination. Tiny yellow coloured crystals were obtained. Amino acids (BDH) were used without purification.

For the determination of association constants, the FZD and amino acids were mixed usually in the ratio 1 : 1 and the mixed solution and the blank solutions were kept at a desired temperature to attain equilibrium. The absorptivity values were measured at different temperatures namely 293, 298, 303 and 308 K. UV - visible spectrophotometer, UV - 2600, Shimadzu model was used for measuring absorptivity.

RESULTS AND DISCUSSION

Furazolidone, was synthesised as a crystalline yellow powder with solubility in water. Satisfactory elemental analysis was obtained (Table 1). It absorbs strongly in the UV region. The maxima near 210 nm appears to be $\pi \rightarrow \pi^*$ transitions where as those near 290 nm appear to be due to $n \rightarrow \pi^*$ transition. The addition of FZD to animo acids changes the absorption maxima (Fig. 1).

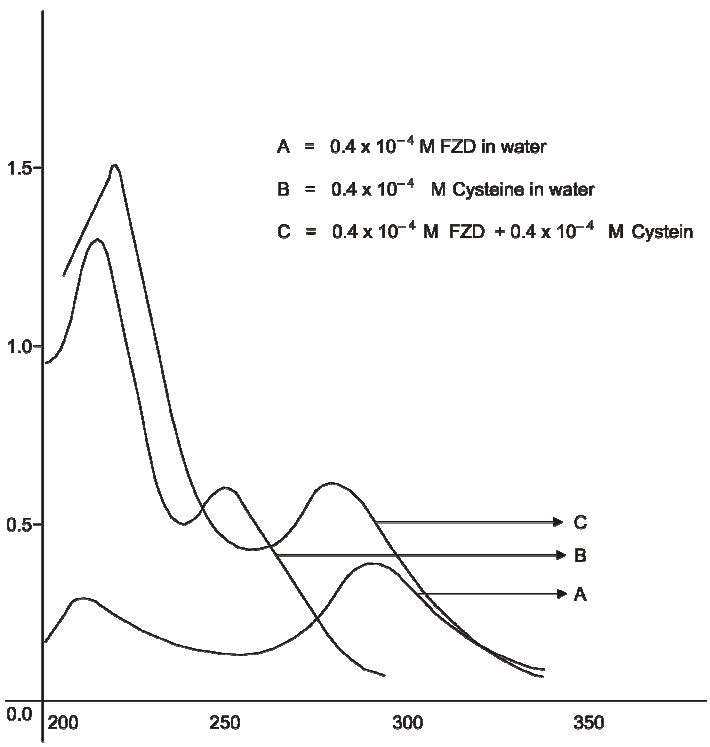

Fig. 1 : Absorption v/s wave length (nm)

Table 1. Elemental and absorption maxima of amino acids, FZD and their complexes

Compound	Element (%) (Found/ Calc.)			λ_{max} (nm)	Isoelectric point
	N	C	H		
FZD	19.7	39.4	3.2	210	—
	19.5	39.2	3.0	290	
Cysteine	11.5	29.7	5.7	250	5.02
	11.4	29.8	5.5		
Histitline	27.2	46.7	5.1	211	7.59
	27.0	46.9	5.0		
Tyrosine	7.7	59.6	6.13	274	5.67
	7.4	59.3	6.3		
Tryptophan	13.7	64.7	5.8	280	5.88
	13.9	64.5	5.5		
FZD-Cys	17.7	37.9	3.7	280	—
	17.9	37.7	3.5		
FZD-His	24.1	44.6	3.7	220	—
	24.2	44.4	3.6		
FZD-Tyr	14.8	51.0	4.2	292	—
	14.6	51.2	4.1		
FZD-Try	17.5	54.1	4.2	290	—
	17.2	54.2	4.3		

Assuming ΔH^0 to remain constant in the temperature range studied (293-308 K), ΔH^0 has been obtained from the slope of the plot of log K against 1/T. The linearity of the plot indicated the validity of the assumptions[7]. The observations of Table 2 reveal that the drug reacts with amino acids in the order : tryptophan > histidine > tyrosine > cysteine. The reactions are instantaneous and the solutions can be kept for several hours. However, the sequence of equilibrium constant cannot be correlated with either pk_1 or pk_2 of the amino acids nor with the isoelectric point.

Table 2. Thermodynamic and other constants for complexes of FZD with amino acids in aqueous medium

Amino acids	Temp (K)	K_{AD} (dm^3 mol^{-1})	ΔH^o (KJ mol^{-1}) 298 K	ΔG^o (KJ mol^{-1}) 298 K	ΔS^o (J deg K^{-1}) 298 K
Cysteine	293	199.1	-22.32	-13.20	-32.02
	298	185.2			
	303	172.1			
	308	120.2			
Histidine	293	269.2	-28.14	-14.32	-50.22
	298	251.4			
	303	194.2			
	308	162.1			
Tyrosine	293	240.2	-27.21	-14.10	-45.12
	298	195.2			
	303	161.2			
	308	140.2			
Tryptophan	293	475.6	-39.14	-15.10	-70.32
	298	305.2			
	303	255.4			
	308	200.2			

It is difficult to ascertain the nature of the complexes. As complex formed and the drug absorb in the same region, it is difficult to identify the band and the spectrum of the complex is deceptive due to the superimposition of bands[8]. Though the absorption maxima of complexes is different; a red shift was observed for the amino acids on complexation. Regarding the IR spectra additional bands at 1610-1630 cm^{-1} (in FZD + Amino acids) were observed which showed the complexation, besides the original (C=N) (1625) band of the drug[9]. The bands at 3340 and 2590 cm^{-1} were assigned to the OH and COOH groups, but no variation was observed because of their non-participation in coordination[10,11].

The interaction between the drug (FZD) and amino acid is spontaneous and

exothermic in character and the reactions, as expected are accompanied with decease in entropy values due to association of drug and amino acids. But this leads to the increase in $\Delta G^0_{(298)}$ values. The enthalpy changes of the complexes and the entropy (Table 2) decrease in the following order: Tryptophan > Histidine > Tyrosine > Cysteine.

Pharmacokinetics

It is the quantitative study of the drug movement in through and out of the body.

(i) Clearance (CD): It is the theoretical volume of plasma from which the drug is completely removed in unit time.

CL = Rate of elimination/concentration

(ii) Plasma half life ($t^{1/2}$)

where V is the total dose administered/ plasma concentration

Therefore, $t^{1/2} = 0.693 \times 150 = 3.465 \approx 3$

Nevertheless, a simple and useful guide to the sojourn of the drug in the body is $3t^{l/2}$ = 87.5% (50 + 25 + 12.5), so this much drug is eliminated.

Pharmacodynamics

It is the study of drug effects and attempts to elucidate the complete action - effect sequence and the dose-effect relationship.

Dose - response relationship : It is given by

$$E = \frac{E_{max} \times [D]}{K_D \times [D]}$$

Where E = Observed effect of a dose [D], E_{max} = maximal response and K_D = dissociation of drug - receptor complex which is equal to the dose of drug at which half maximal response is produced.

It the dose is plotted on logarithmic scale, the curve becomes sigmoid and a linear relationship between log of dose and the response (as shown in Fig. 2) is obtained.

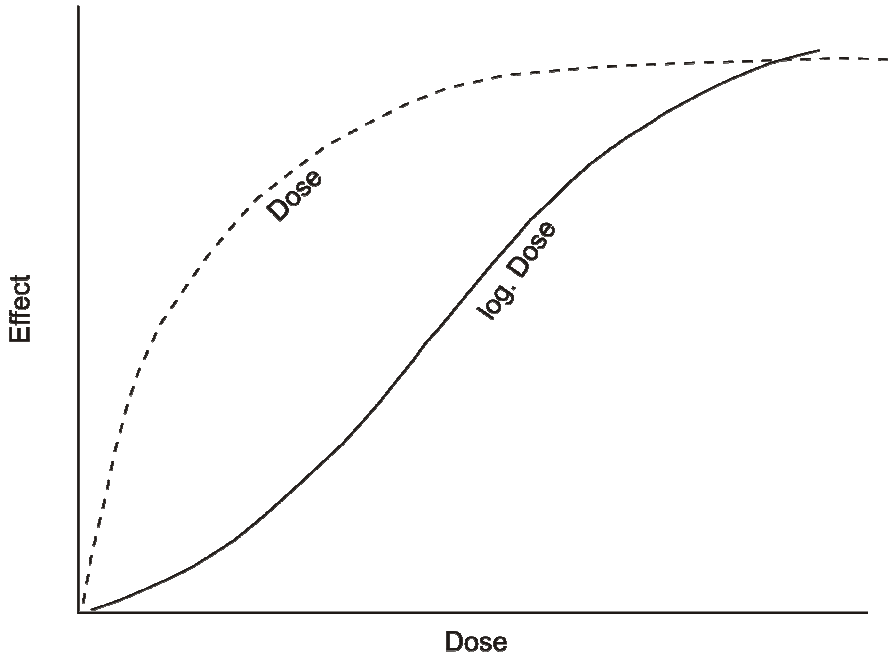

Fig. 2: Dose response and log dose-response curves

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