Pakistan Journal of Pharmaceutical Sciences
5(1) 47-54 (1992)

EFFECT OF VISCOSITY AND BUFFER SALTS ON THE STABILITY OF SULPHACETAMIDE SOLUTIONS

TAUQIR AHMAD
Department of Pharmaceutical Chemistry,
University of Karachi, Karachi-75270, Pakistan

ABSTRACT

A study of identification and fate determination of degradation products of sulphacetamide in aqueous solutions during UV irradiation and thermolysis at 70°, 80° and 90°C u made. The effect of viscosity sod buffer salts in presence of antioxidants on the rate of hydrolysis in investigated. An increase in the viscosity of solution results in a decrease in the rate of hydrolysis. Similar viscosity effect has been observed on the photolysis of sulphacetamide solutions No significant salt effect on the rate of hydrolysis of sulphacetamide in citrate and phosphate buffer (pH 7.4) has been noticed. The thermodynamic parameters E_a., ΔH, ΔS for the reaction have been determined.

Introduction

Sulphacetamide ophthalmic preparations available under various proprietary names are made isotonic in aqueous medium containing buffers, stabilizers and preservatives. These preparations are used as 5 to 30% drops or washes in the treatment of corneal ulcers, acute conjunctivitis and in prophylaxis of ocular infections after injuries or burns. The effectiveness of these formulations for eye diseases depends on the correct choice of buffers, stabilizers and viscosity imparting agents.

The photolysis of sulphacetamide and sulphanilamide at various pH has been investigated by Whittet (1949, 1950), Fletcher and Norton (1963) and Clarke (1965). Pandula, Racz and Pajor (1969) have reported the photochemical degradation of sulphacetamide to azo and azoxy derivatives. Several workers have studied the thermal and photodegradation of sulphacetamide under different conditions (Anderson, 1966; Davies *et a1*., 1970; Ahmad, 1981).

In the present investigation studies have been conducted to assess the hydrolysis of sulphacetamide solution to sulphanilamide and subsequent oxidation to azobenzene-4,4'-disulphonamide. This study was crried out in the presence or absence of antioxidants. The viscosity effects in phosphate or citrate buffers were studied under different conditions of temperature and exposure to UV radiation.

Materials and Methods

Sulphacetamide and sulphanilamide were obtained from Sigma (USA). azobenzene-4,4'disulphonamide was prepared by the method of Seikel (1940). Antioxidants and all other materials used in this study were of analytical grades and obtained from BDH and Merck.

In ultraviolet irradiation experiments, 10^{4}M sulphacetamide/ sulphanilamide, buffered / unbuffered solutions at pH 7.0, with or without antioxidants were prepared. These solutions were deoxygenated by bubbling nitrogen and were exposed to a 30 watt UV tube emitting 88.7% of radiations at 254 am. Sulphacetamide solutions were also exposed to 40 watt lamp for 1000 hours. Aliquots of the photolysed solutions were subjected to chromatographic examination and spectrophotometric assays at periodic intervals. A multicompment spectrophotometric method was carried out for quantitative assays of sulphacetamide, sulphanilamide and azobenzene-4,4'-disulphonamide. The following values of molar extinction coefficients ($mole^{-r}$ cm^{-r}) were used. Sulphacetamide, 258 mu = 13500, 268 am = 17100, 320 nm = 100. Sulphanilamide, 258 um = 15300, 268 mm = 11600, 320 um = O. Azobeuzene-4,4'-d sulphonamide 258 nm = 3100,268 am = 3900, 320 um = 13200. The reproducibility of the assay method determined for the known mixtures of these compounds was of the order of ± 5%.

In thermolysis experiments amber glass ampoules were filled with $10'^{3}$M sulphacetamide or sulphanilamide solutions and sealed. These were heated in oven for 300 hours at 70°, 80°, and 90°C with t 1% fluctuation. The samples were cooled with ice to room temperature and subjected to chromatography and spectrophotometry.

In viscometry experiments sulphacetamide solutions containing several antioxidants viz, sodium metabisulphite (0.095% w/v), sodium sulphite (0.063 % w/v), sodium thiosulphate (0.124 % w/v), thiourea (0.038% w/v) and ascorbic acid (0.088% w/v) in sodium and potassium phosphate and citrate buffers at pH 7.4 were used. Cannon Fenske Viscometer of capillary No.100 (constatn 0.01585) and German Thermostat bath with ± 0.01°C accuracy were employed for flow time measurement at various temperatures. The viscosity (ηo) is calculated by using the equation no = d_oK (t_o-C_o) where d_o = density of control, K = 0.01585, t_o = flow time of control solution in sec. C_o = Haggenbach correction.

Results and Discussion

Thin layer chromatography of UV irradiated and heated sulphacetamide solutions (pH 7.4) showed the presence of sulphanilamide, azobenzene-4,4' - disulphonamide and several unknown products (Table 1). The azobenzene-4,4' - disulphonamide is detectable after heating for 200 hours at 70° to 90°C. The gradual decrease in the absorption of UV irradiated and heated solutions of sulphacetamide at 268 nm and simultaneous increase in absorption at 258 um as well as in the 280-300 nm region is in accordance with the absorption characteristics of sulphanilamide and azobenzene-4,4' disulphonamide respectively (Ahmad, 1989). Azo derivative of sulphanilamide has absorption similar to that of azobenzene in having the band characteristic of n + it transitions. The hydrolysis of sulphacetamide to sulphanilamide is a first-order reaction and the oxidation of sulphanilamide to azo derivative is a second-order reaction (Table 2). The over all rate of hydrolysis of sulphacetamide is found to be independent of buffer species during heating.

Table 1

TLC of photolysed* and heated solutions of sulphacetamide containing antioxidants at pH 7.4 (citrate buffer)

Antioxidants	Degradation products				
Nil	S_1	Azo	Sc	u_1-u_4	u_9- u_{10}
Sodium sulphite	"	"	"	"	"
Sodium thiosulphate	"	"	"	"	"
Sodium metabisulphite	"	"	"	"	"
Thiourea	"	"	"	"	"
Ascorbic acid	"	"	"	"	"

*Photolysis for 8 hours. Sulphacetamide (R_f 0.86), S_1 = sulphanilamide (R_f 0.76), azo = azobenzene-4,4'-disulphonamide (R_f 0.43), Sc = sulphanilic acid (R_f 0.0), u_2 = Brown Product (R_f 0.66), u_3 = (R_f 0.3), u_1, u_4, u_9, u_{10} (unknowns of low R_f, less intense), u_{10} (Rf 0.22); Solvent system: n-butanol: acetic acid: water: 65: 15: 20/Silica gel. G/UV 254 nm.

Table 2

Rate constants[+] for the photodegradation of sulphacetamide and sulphanilamide at pH 7.4 (citrate buffer)

Antioxidants	Sulphacetamide k_1S_o (min^{-1}•)	Sulphanilamide k_2S_1($1.mol^{-1}$ min^{-1})
-	$4.0x\ 10^{-3}$•	$2.40x\ 10^{-3}$
-	$1.68x\ 10^{-10}$••	1.36×10^{-1}
-	1.20×10^{-3}	$3.70x\ 10^{-3}$
Sodium metabisulphite	$1.0x\ 10^{-4}$	$0.74x\ 10^{-3}$
Sodium sulphite	1.2×10^{-4}	0.83×10^{-3}
Sodium thiosulphate	1.3×10^{-4}	1.02×10^{-3}
Thiourea	1.8×10^{-4}	0.53×10^{-3}
Ascorbic acid	2.1×10^{-4}	0.61×10^{-3}

•Unbuffered solutions exposed to 30 watt UV lamp.
••Unbuffered solutions exposed to 40 Watt Tungsten lamp.
S_o = Sulphacetamide, S_1 = Sulphanilamide
[+]Error = ± 5%

The activation energy (E.) of the hydrolysis reaction at pH 7.4 is 12.79 K cal. mol^{-1}. Other thermodynamic parameters, enthalpy and entropy are shown in Table 3. A higher activation energy would indicate greater stability of the molecule to temperature. The photolysis of sulphacetamide may represents a complex system which involves a set of reactions leading to the formation of a large number of degradation products (u_1 to u_{10}) through sulphanilamide as an intermediate. The rate constants for the hydrolysis of sulphacetamide in presence of antioxidants are reported in Table 2. It may be concluded that in the photolysis of sulphacetamide, sodium metabisulphite is the most effective antioxidant followed by sodium sulphite, sodium thiosulphate, thiourea and ascorbic acid in decreasing order of activity. The values of the rate constants calculated in relation to the molar concentration of the antioxidants also lie approximately in the same order.

Table 3

Thermodynamic parameters for the hydrolysis of sulphacetamide solutions at pH 7.4

Activation energy (E_a)	12.79 K Cal. $mol^{-1.}$
Frequency Factor (A)	1.73×10^7 $min^{-1.}$
Enthalpy (ΔH)	12.12 K. Cal. $mol^{-1.}$
Entropy (ΔS)	-55.18 $Cal.deg^{-1}. mol^{-1.}$

Table 4

Effect of viscosity on the thermal degradation of sulphacetamide at pH 7.4

Buffer	Temperature (^oC)	Rate constants k_1, min^{-1}	Viscosity (Cp)
Sodium citrate	32	0.355×10^{-5}	0.992
	40	0.549×10^{-5}	0.972
	50	0.977×10^{-5}	0.894
Potassium Phosphate	32	0.360×10^{-5}	0.988
	40	0.551×10^{-5}	0.974
	50	0.980×10^{-5}	0.902

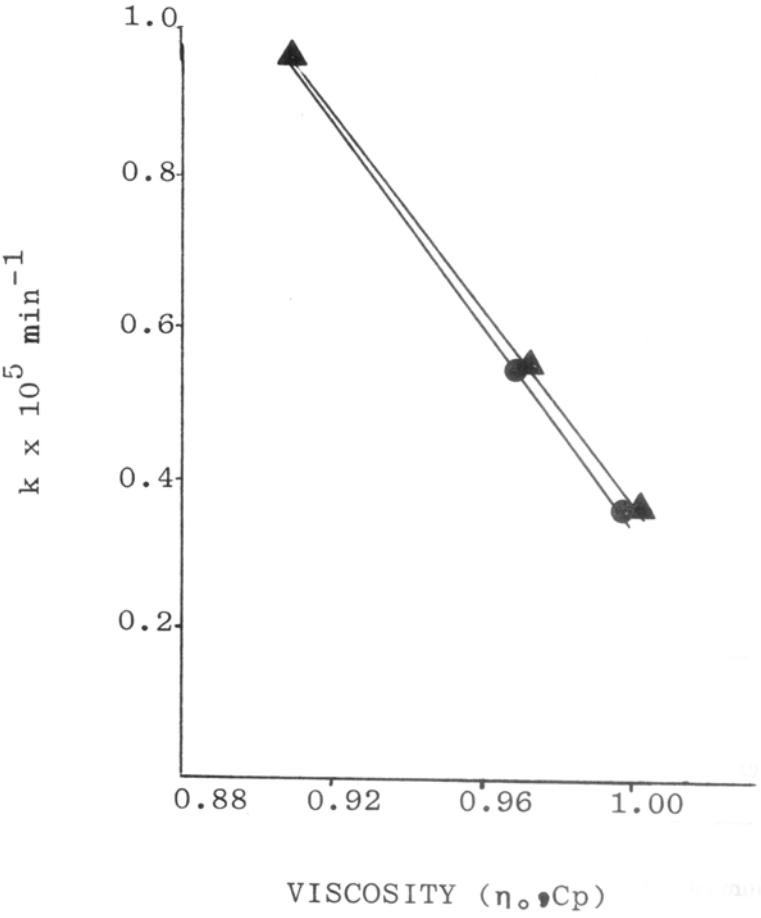

Figure 1. Effect of viscosity on the thermal degradation of sulphacetamide solution at pH 7.4, —●— citrate buffer, —▲— phosphate buffer.

The effect of viscosity on the stability of sulphacetamide solutions at pH 7.4 (citrate and phosphate buffer) is shown in Figure 1 (Table 4). The rate of hydrolysis of sulphacetamide is linearly related to the viscosity of the solution. Thus the presence of viscosity imparting agents in eye drop preparations may not only facilitate drug retention but also the stability of the solutions. This has also been observed in the case of photolysed solutions. The viscosity considerations in the formulation of ophthalmic preparations may improve the shelf life of drugs undergoing hydrolysis and oxidation.

Acknowledgements

This work was financially supported by National Scientific Research and Development Board, University Grants Commission, Islamabad. I am very grateful to Mr. M. Afzal, Director Academia and Dr. M.H. Qazi, Secretary, U.G.C., Islamabad for their interest and cooperation in this project. I am also grateful to Professor Dr. Iqbal Ahmad for his help in this project. Finally, I am thankful to my students Mr. Safeer Haider, Mrs. Shamim Akhtar and Miss Farzana Hassan who have collaborated in this project.

References

Ahmad, T., Ahmad, I. (1981). Degradation studies on sulphacetamide eye drops. *Pharmazie*., **36**: 619-621.

Ahmad, T., Ahmad. (1989). Photo-oxidation of sulphanilamide to no and azoxy compounds. *Pak J. Pharm Sci.,* **2**(1): 1-5.

Anderson, R.A. (1966). Hydrolysis of sulphacetamide solutions at sterilization temperature. *Aust. J. Pharm.,* **47**: 555.

Clarke, PA. (1965). Decomposition of sulphacetamide sodium eye drops. *Pharm J.*, **194**: 375-376.

Davies, DJ.G., Meakin, BJ, Moss, S.H. (1970). The effect of antioxidants on hydrolytic and oxidative degradation of sulphacetamide in aqueous solutions. *J. Pharm Pharmacol,* **22**: 43S-52S.

Fletcher, G., Norton, NA. (1963). Eye drops of sulphacetamide. *Pharm J*., **191**: 145-147.

Pandula, E., Racy I, Pajor, Z. (1969). Uber die zersetzung and stabilisierung von sulphacetamid-natrium in Arneizubereitungen. *Phazmazie*, **24**: 155-157.

Seikel, M.K (1940). Oxidation Products of sulphanilamide. *J. Am. Chem. Soc*., **62**: 1214-1216.

Whittet, T.D. (1949). Notes on sodium sulphacetamide eye drops. *Pharm. J*, **163**:

177-179.

Whittet, T.D. (1950) Stability of sulphonamide Injections. *Pharm. J*, **165**: 147.