Stability of Suiphacetamide Eye drops at Higher Temperature

Pages with reference to book, From 168 To 172

Tauqir Ahmad (Department of Pharmaceutical Chemistry, University of Karachi.)

Abstract

Suiphacetamide solutions at higher temperature degrade to its hydrolysed product, sulphanilamide, with a first-order rate constant. The degraded products are identified and characterised by chromatography and spectrophotometry. Attempts are made for the evaluation of kinetics, entropy and enthal changes activation energy and frequency factors during heating of sulphacetamide solutions. The determination of these thermodynamic elements is useful in prediction of the stability of suiphacetamide eye-drop formulation at elevated temperatures (JPMA 33: 168, 1983).

Introduction

Suiphacetamide solutions in different concentrations ranging from 5 to 30% are used as ophthalmic drops for various eye infections. In the study of the stability of suiphacetamide eye-drops, many workers, Whitter (1949, 1950), Anderson and Maudson (1963), Fletcher and Norton (1963), Dickenson (1963) have studied the effects of temperature during sterilization and autoclaving of ampoules. On heating at 100-120°C, sulphacetamide solutions get hydrolysed into sulphanilamide which crystallise on cooling. The loss 1.5 to 1.0% occurs in suiphacetamide concentration during heating between 100-120°C (Anderson, 1966; Davies et al., 1970). Clarke (1967) suggested the prevention of crystallisation of sulphanilamide during sterilization by buffering the solution of suiphacetamide at pH 9 to 9.5. According to Kulesh and Bugrim (1968) at 100°C showed no colour change even after one year of storage.

In this investigation, stability of sulphacetamide solutions has been checked between pH 1 to 13 at 70°, 80° and 90°C for 12-15 days. The degradation products have been identified by chromatography and spectrophotometry. The kinetics, activation energy, frequency factor, enthalpy and entropy changes are determined during heating of suiphacetamide solutions.

Material and Methods

5ml portions of 10^{-2}M buffered solutions of pure crystalline sulphacetamide (Sigma, USA) of pH 1 to 13 are filled and sealed in amber glass ampoules. These ampoules are boiled twice for one hour in water, before being filled with sulphacetamide solutions, to remove any trace of alkali, and are finally placed in an oven adjusted to 70°, 80 and 90 with ± 1 C fluctuations in tempera ture. Samples are removed at suitable intervals chilled in ince to stop the reactions are examined by chromatography and spectrophotometry.

Results

(i) Chromatographic Identification: Thermally heated samples are chromatographed on the fluorescent silica gel G 254 and alumina layers. The solvent systems T_1 to T_{10} have been employed (Table I)

Table I R_f values in TLC of Sulphacetamide and Its Decomposition Products.

Compounds*	Solvent Systems**									
	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8	T_9	T_{10}
Sulphacetamide	0.85	.85	.85	.86	0.82	0.86	0.28	0.24	0.86	0.49
Sulphanilamide	0.79	.77	.81	.76	0.83	0.84	0.81	0.40	0.76	0.85
Azobenzene-4,4' -disulphonamide	0.18	.42	.84	.43	0.77	0.74	0.93	0.48	0.67	0.91

*Spots and their shapes are detected under uv light, iodine vapours and Bratton-Marshal reagent.
Sulphacetamide, sulphanilamide = round spots

and the degradation products are detected either under the UV light at 254nm and 320nm or sprayed with iodine vapours or Bratton-Marshall reagent.

(ii) Spectrophotometric Determinations:

(a) Synthetic Mixtures and Extinction Coef-ficients:

Synthetic mixtures of authentic suiphacetamide, sulphanilamide, and azobenzene-4, 4' -dis
Azobenzene-4, 4' - disulphonamide = elongated spots

Absorbents and solvent systems:

T_1 to T_6 = silica gel and flourescent silica gel G_{254}

T_7 toT_{10} = Alumina - H

T_1 = n-butanol-acetic acid-water (50-15-35)

T_2 n-butanol-acetic acid-water (100-20-48)

T_3 = 3.7% aq. citric acid-n-butanol (13-87)

T_4 = n-butanol-acetic acid-water (65-15-20)

T_5 ethanol-methanol (50-50) Kho and Klein[10]

T_6 0.05N HCL-n-propanol (20-80)Kho and Klein[10]

T_7 = n-butanol-water (90-9) Wandal[11]

T_8 chloroform-methanol (80-15) Kamp[12]

T_9 = Strong ammonia-methanol (1.5-100) Sunshine [13]

T_{10} methanol-water (96-8)Wandal[11]

ulphonamide are prepared. The concentration of each component in a mixture is measured on a Pye Unicam SP 500 spectrophotometer and evaluated by solving the simultaneous equations. The % error of reproducibility of the mixture analysis technique lie with in ± 4 '%. After confirming the validity of Beer's law, the molar extinction coefficients, € $Imol^{-1}$ cm^{-1} of sulphacetamide, sulphanilamide and azobenzene -4, 4' -disulphonamide at pH 4.0 are determined by using the least square method. The value of molar extinction coefficients at 258, 268 and 320nm are given below.

Sulphacetamide:

at 7 258 (max) = 13.530 X iø; at7265
(max) = 17.132 X 103;att32ô=0. 1 X 10-3

Suiphanilamide:

€ at 7 258=15.254 X i0; at7268= 11.632X io; at7 320 =0.106 X103

Azobenzene -4, 4' -disuiphonamide:

€at 7 258=3.128 X io; at7 26s = 3.945 X iø; att32(max)= 13.15 X 10-3

Known dilutions of heated solutions of sulphacetamide with buffer of pH 4.0 are made and the absorbance values are measured. The concentrations of suiphacetamide and sulphanjlamjde in heated solutions have been calculated by solving the simultaneous equations. Analysis is carried out at pH 4.0 because a distinct difference in the absorption maxima of both suiphacetamide, 7% max 268nm, and suiphanilamide, 7max 258nm, exist.

(b) Characteristics of suiphacetamide and its decomposition products:

Sulphacetamide : m.p. 184°C (lit. (Clarke, 1969) m.p. 181-184°C; Rf.O.42 (chloroform : ethyl alcohol : heptane, 1:1:1) (lit. (Klein and Kho, 1962) Rf.O.42); UV aq79 (max) 259nm (log € 4.24) lit. Bohme and Wanger, 1942) max 260nm;IRKBrV max 1320, 1155 (S=0, stretching), 1585 (-NH deformation) and 1680cm' (-CoCH3 stretching). The values are in agreement with those of Clarke (1969) and Bellamy (1964). Suiphacetamide : m.p. 166°C (lit. Clarke, 1969) m.p. 164.5° - 166.50C); Rf. 0.53 (Chloroform ethyl alcohol: heptane, 1: 1: 1) (lit. Klein and Kho, 1962) Rf. 0.53; Tmax (pH 7) 258 nm (loge 4.18) lit. Elvidge, 1941) 7max 259nm; IR. (KBrv max 1310, 1150 (s=o stretching) and 1591 cm' (-NH deformation). The frequencies values are in agreement with those of Clarke (1969). Azobenzene -4, 4' -disulphonamide:m.p.311C dec. (lit. (Seikel, 1940) 312°C dec.); Rf.O.17 (n-butanol: acetic acid: water, 50:15 :35) (lit. (Clarke, 1969) T max336cnm); IRKBrV max 1350, 1170 (S=0 stretching Rf. o.17); /max (0.1 N NaOH) 336nm (log C 4.16) (lit. Pondula, 1969) / max 3 36nm) ; and 1410cm', N=N stretching).

Discussion

It is known that suiphacetamide solutions at high temperatures facilitate hydrolysis leading to the formation of suiphanilamide and the behaviour of these thermo-chemical reactions have been studied by many workers (Whittet, 1949, 1950; Fletcher and Norton, 1963; Anderson, 1966; Davies et al., 1970). The chromatographic examination of the heated ,solutions of suipha- -3.0 cetamide showed the presence of sulphanilamide -4.O and azobenzene-4,4' -disuiphonamide. The chrornatographic separation of the decomposition products of sulphacetamide leads to the develop- ment of a multicomponent spectrophotometric analysis. The gradual decrease in the absorption of heated solutions at 268nm of suiphacetamide and simultaneous increase in absorption at 258nm and in the region of 280-300nm is in accordance with the absorption characteristics of suiphanilamide formation and coloured azobenzene -4,4' -disulphonaniide. The presence of azo derivative of sulphanilamide is detectable after atleast 200 hours of heating between 70° to 90°C of suiphacetamide solutions at pH 5-11. Azo derivative of suiphanilamide is similar to azobenzene in having the band characteristic to it -p transitions. In the light of experimental observations and kinetic data calculated in present study, the following scheme may be proposed for degradation of suiphacetainide (S0) (Ahmäd) 1978). Sulphacetamide k1 -+ Suiphanilamide (S1) k2 -p Azo deriv. The hydrolysis of suiphacetamide (S0) to suiphanilamide (S1) is a first-order (k1) reaction and the oxidation of (S1) to azo derivative is a second-order(k2) reaction (Fig. 1).

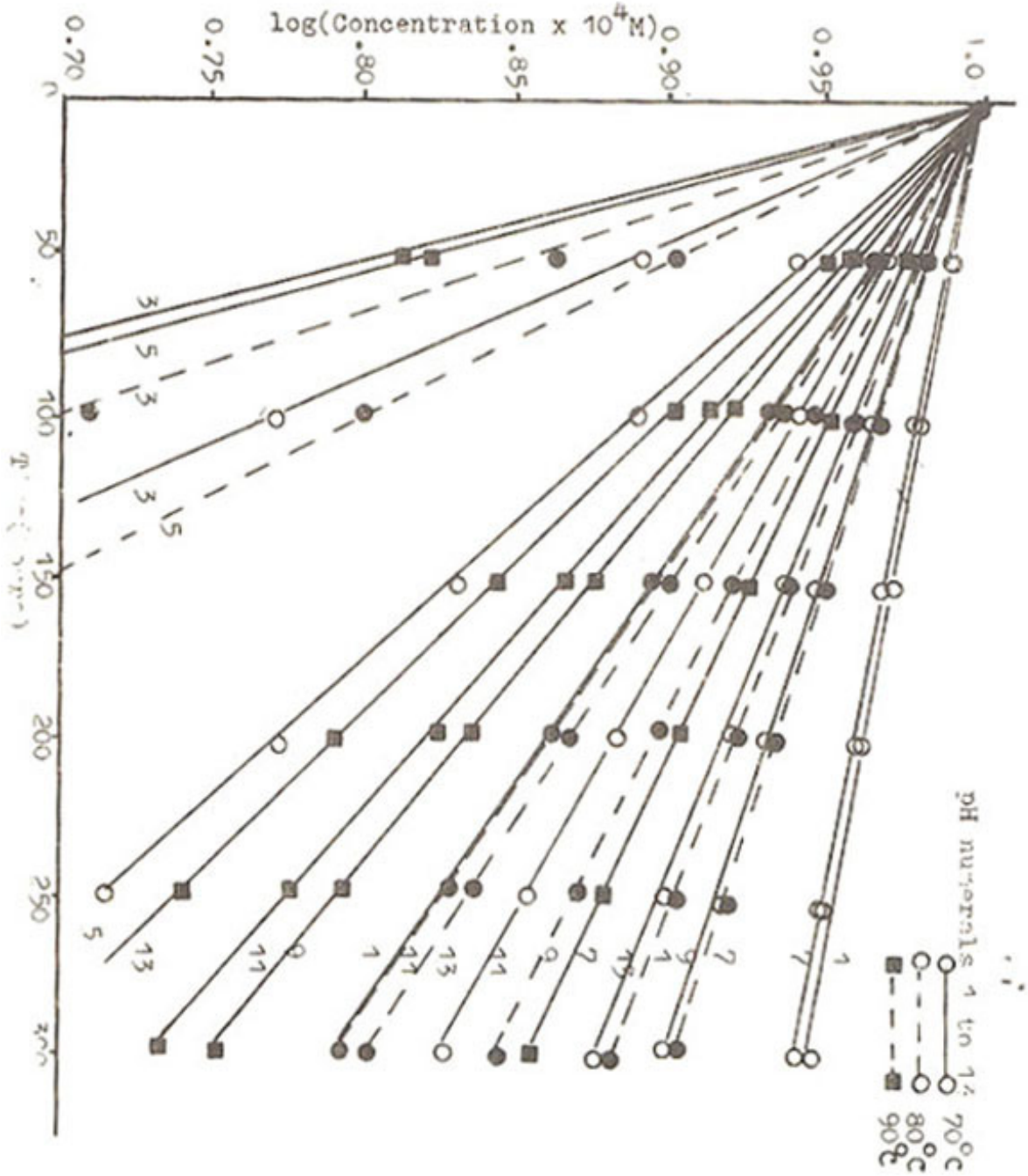

Fig.1. First-Order plots for 10^{-3}M Sulphacetamide at 70°, 80° and 90°C

The overall rate of hydrolysis of sulphacetamide is found independent during heating, some fluctuations in rate values are possible towards strong acidiclalkaline media which may be due to ionic mobilities of The molecules (log-pH profiles in Fig.2).

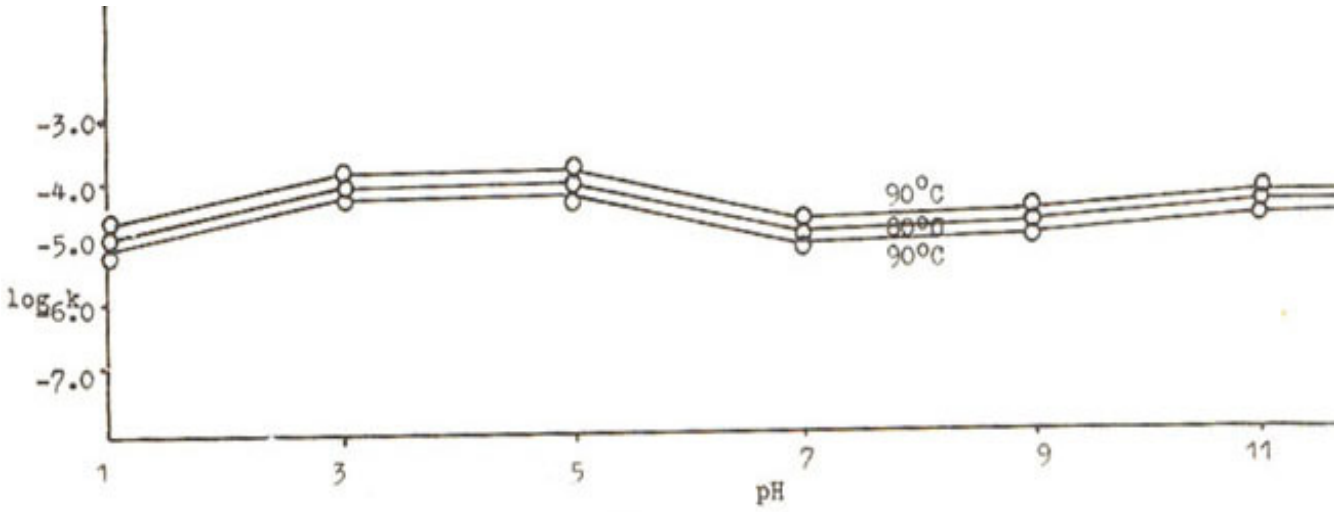

Fig.2. log k-pH profiles of 10^{-3}M solutions of sulphacetamide.

The activation energy expresses the influence of temperature on reaction velocity. The reacting molecules must acquire this energy in order to undergo degradation. The higher the value for the energy of activation the greater is the stability of the substance to temperature. In addition the frequency factor determination also help in determining the frequency of collisions which is expected between the reacting molecules for a given reaction. The values of activation of energy factors for the sulphacetamide solutions (103M) at pH 1 to 13 have been determined by the use of Arrhenius equation K = A e EIRT where K, is specific rate of degradation,

Table -II Thermolysis of 10^{-3}M Sulphacetamide Solutions

pH	Enthalpy change ΔH(k.cal. Mole^{-1})	Entropy change ΔS (eal. deg^{-1} mol.$^{-1}$)	Activation energy E (k. cal. mole^{-1})	Frequency factor A(min.$^{-1}$)
1.	14.86	- 47.19	15.630	2.056×10^{9}
3	12.12	- 50.38	7.968	0.010×10^{7}
5	14.13	- 45.71	15.060	1.440×10^{9}
7	12.12	- 55.18	12.790	1.731×10^{7}
9	10.57	- 58.56	11.370	0.706×10^{7}
11	7.80	- 65.51	8.530	0.016×10^{7}
13	10.60	-58.03	11.370	0.793×10^{7}

A, is frequency factor (Table II) E, is activation energy, also called AF, free energy of activation (Table II), R, is gas constant (1.987 calories degree ‘mole 1), T, is temperature in degree absolute.
The entropy and enthalpy changes are also calculated for the suiphacetamide solutions at different temperatures (Table II and Fig. 3,4).

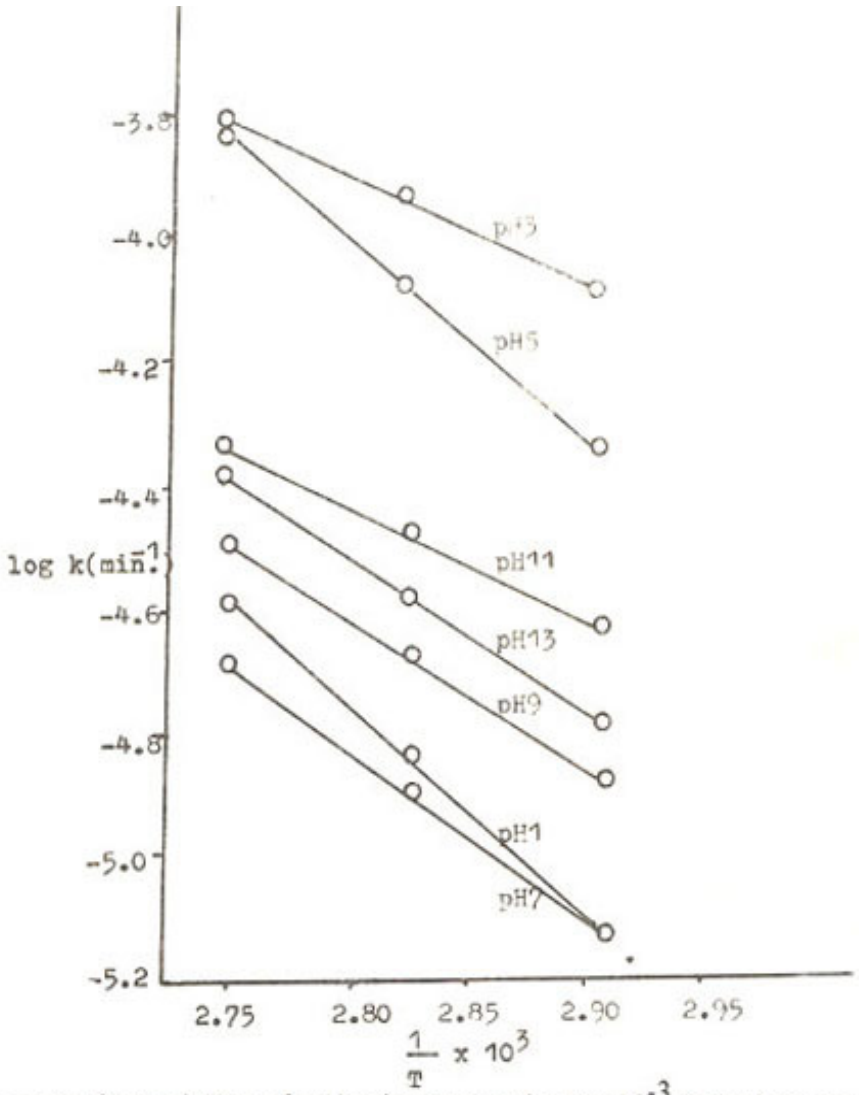

Fig.3. Arrhenius plots for the determintion of activation energy for the 10^{-3}M sulphaectamide solutions.

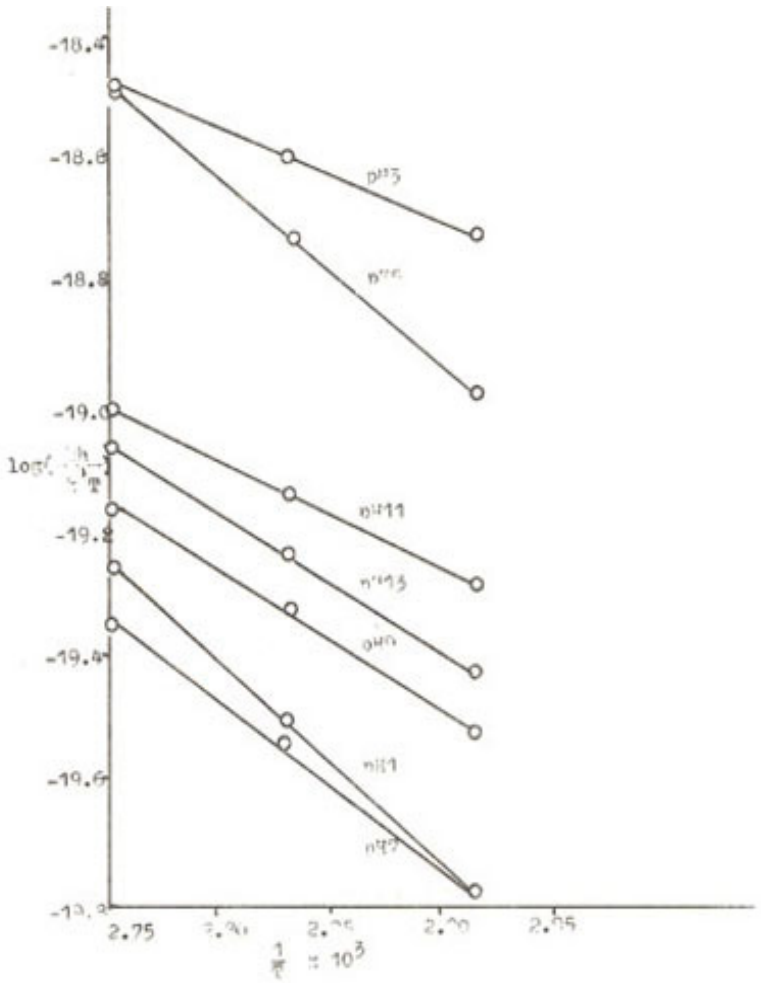

Fig.4. Arrhenius plots for the determination of enthalpy and entropy changes of activation for the 10^{-3}M sulphacetamide solutions.

The values calculated for activation of energy (E) for suiphacetamide solution of pH 1 to 13 lie in the range of 8 to 15 K. cal. mole' The lower values of activation energy (Relatively) of suiphacetamide are obtained at pH 3 and pH 11, showing relatively less stable species of molecules which may be due to catalytic effect of buffer ions at these particular pH values.

References

1. Anderson, R.A. and Maudson, J.W. (1963) The discoloration of sodium suiphacetamide solutions. Aust. J. Pharm., 44: 518, S138.
2. Anderson, R.A. (1966) Hydrolysis of sulphacetamide solutions at sterilization temperatures. Aust. J. Pharm., 47 555.
3. Ahmad, T. (1978) Ph. D. Thesis, Kar. University.
4. Bellamy, L.J The Infra-red spectra of complex molecules. New York, Wiley 1964.
5. Bohme, H. and Wagner, J. (1942) Absorption spectra of pharmaceutically important sulfonamide derivatives. Arch. Pharm., 280 : 255.
6. Clarke, P.A. (1967) Sulphacetamide Eye.drops. Pharm. J., 199 :4 14.
7. Clarke, E.G.C. Isolation and Identification of drugs in pharmaceuticals, body fluids and postmartem material. London, Pharmaceutical Press, 1969.
8. Davis, D.J., Meakin, B.J. and Moss, S.H. (1970) The effect of antioxidants on the hydrolytic and

oxidative degradation of suiphacetamide in aqueous solution. J. Pharm. Pharmacol., Suppl. 438.
9. Dickenson, H.E. (1963) Cited by Fletcher, G. & Norton, D.A. Pharm. J., 191 : 147 (Ref. 10).
10. Elvidge, W.F. (1941) Absorption spectrophotometry in Pharmaceutical Analysis. Part-3.
11. Fletcher, G., Norton, D.A. (1963) Eye-drops of suiphacetamide. Pharm. J., 191:145.
12. Klein, S. and Kho, B.T. (1962) Thin-layer chromatography in drug analysis. I. Identification procedure for various sulphonamides in pharmaceutical combinations. J. Pharm. Sci., 51: 966.
13. Kulesh, K.F. and Bugrim, N.A. (1968) Glaznye kapli vide gotovykin lebkarstvenbykh sredstv. Soobshchenie 1. Sulfatsil restvormui. Farmatsua, 17 : 14.
14. Seikel, M.K. (1940) Oxidation products of sulphanilamide. J. Am. Chem. Soc., 62:1214.
15. Whittet, T.D. (1950) Stability of sulphonamide Injections, Pharm. J., 165 : 309.