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Degradation Kinetics of Sulfacetamide Sodium in Ophthalmic Preparations in Dark and Light

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Abstract: Sulfacetamide sodium is one of the widely used sulfonamide for ophthalmic infections, due to its bactericidal activity, low toxicity and non-irritating ability to eyes at higher doses. It is available in varying concentrations of 5–30% as ophthalmic solutions, suspensions or ointments. The formulations of sulfacetamide sodium are known to degrade on storage and become discolored in appearance. Different ophthalmic preparations (n=5) of sulfacetamide sodium have been subjected to degradation studies in dark and light in order to evaluate their kinetics of degradation. A stability-indicating UV spectrometric method has been used for the assay of the active drug and its degradation products. The identification of pure drug and the degradation products has been made through thin-layer chromatography (TLC). The results indicated that the degradation of sulfacetamide in ophthalmic preparations follows first-order kinetics. Sulfanilamide was found to be the major degradation product in all samples. The rates of degradation of sulfacetamide sodium in different ophthalmic preparations are about 1500 times faster on exposure to UV light than those of the samples stored in the dark. The formulations excipients are also found to influence the rate of degradation.

Key words: Sulfacetamide sodium, Ophthalmic preparations, Kinetics, Degradation, Sulfanilamide.

INTRODUCTION

Sulfacetamide sodium is a sulfonamide antibacterial agent that is mainly used in the treatment of corneal ulcers, acute conjunctivitis and in prophylaxis of ocular infections after injuries or burns. Ophthalmic preparations of sulfacetamide sodium are available under various proprietary names in the form of eye drops or washes, usually in a concentration of 10 to 30%. Sulfacetamide is known to degrade on exposure to light and temperature to sulfanilamide, which is a less potent antibacterial agent than the parent compound (Sweetman, 2009). Therefore, proper storage of the dosage form is extremely important for the optimum efficacy and stability.

Several workers have studied the thermal and photodegradation of sulfacetamide under different conditions (Anderson, 1966; Davies *et al*., 1970; Ahmad and Ahmad, 1981). The photolysis of sulfacetamide and its major degradation product, sulfanilamide, at various pH has been investigated by Whittet (1949), Clarke (1965), Ahmad (1992), Fletcher and Norton (1963), Ahmad and Ahmad (1983), Ahmad and Ahmad (1988), Ahmad and Ahmad (1989a,b) and Ahmad and Ahmad (1990). Pandula *et al*. (1969) have reported the photochemical degradation of sulfacetamide to azo and azoxy derivatives. The mode of degradation of sulfacetamide and the formation and nature of the degradation products are not clearly understood, probably due to the complexity of the degradation (hydrolysis/photolysis/oxidation) reactions. The literature so far available on this subject points out towards a lack of basic work on this problem and warrants a need for systematic investigation of the photodegradation reactions of sulfacetamide, which may provide a rational basis for the stabilization as well as an appreciation of the possible harmful effects of the reaction products. This study has been performed to investigate the degradation pattern of sulfacetamide sodium in the dark and in the light in ophthalmic preparations to give a rationale to pharmaceutical scientists that could help in the stabilization of the active drug in the dosage forms.

MATERIALS AND METHODS

Materials: The different ophthalmic preparations of sulfacetamide sodium were obtained from a local pharmacy of Karachi. All other solvents and reagents used were of analytical grade obtained from Sigma-Aldrich/Merck/BDH.

Storage of ophthalmic preparations: The ophthalmic preparations of sulfacetamide sodium were stored at 30±2°C / 65±5% RH (Model YWER-A1001P, Dongguan Yuanyao Electronics Technology Co. Ltd., China) in their original containers for a

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period of 6 months, protected from light according to International Council for Harmonization (ICH) climatic conditions for zone IV, i.e., hot and humid (ICH, 2003). The samples were assayed for their sulfacetamide and sulfanilamide contents periodically. All experiments were performed in triplicate.

Thin-layer chromatography (TLC): The TLC was performed according to the method and solvent systems, reported by Klein and Kho (1962), Fletcher and Norton (1963), Kho and Klein (1963) and Moffat *et al*. (2011). The brief details are as follows:

Precoated plates of silica gel G / UV 254 (Merck) and alumina H (Type E, Merck) with a layer thickness of 250-µm were used. All experiments were performed at a temperature of 25±2°C. The solvent systems employed included:[1] chloroform-ethanol-heptane (1:1:1, v/v) (Klein and Kho, 1962); [2] n-butanol-acetic acid-water (50:15:35, v/v) (Moffat *et al*., 2011); [3] n-butanol-acetic acid-water (100:20:48, v/v) (Fletcher and Norton, 1963) and [4] Ethanol-methanol (50:50, v/v) (Kho and Klein, 1963). The spots were sprayed with different reagents for the identification of products and examined under UV light at 254 and 365 nm (Uvitech lamp, UK).

pH measurement: The pH of the ophthalmic preparations was measured using a digital pH meter (Elmetron, model: CP-501, Poland), to which a combination electrode and a temperature probe were attached. The sensitivity of the instrument was ±0.01 pH units. The routine calibration of the instrument was performed, using buffer tablets of pH 4.00 and 7.00 (Merck). Each preparation was emptied in a 5 ml Pyrex beaker and the electrode along with temperature probe was immersed directly into it to record the pH.

Assay of sulfacetamide sodium and degradation product: A two-component stability-indicating UV spectrometric method reported by Ahmed *et al.* (2017) for the assay of sulfacetamide sodium and its major degradation product, sulfanilamide, in pure and ophthalmic preparations has been applied. Appropriate dilutions of the ophthalmic preparations (10,000 for 10% and 20,000 for 20%) were made with distilled water and the pH was adjusted to 4.0 with 0.2 M of acetate buffer to achieve the required concentration for the assay. In addition, the ophthalmic suspensions containing other active drugs, such as, prednisolone acetate (0.2%) and phenylephrine HCl (0.12%), were filtered to remove their insoluble ingredients. The filtration, followed by dilution, was found adequate to remove these drugs and hence interference from the analysis (Ahmed *et al.*, 2017). The absorbencies of the diluted solutions were measured at 271 and 258 nm for sulfacetamide sodium and sulfanilamide, respectively, using 10 mm path length quartz cuvettes on a calibrated UV-visible spectrometer (Shimadzu UV-1601, Japan).

Photodegradation of the ophthalmic preparations: All ophthalmic preparations of sulfacetamide sodium were exposed to UV light (TUV Philips 36 watt tube, 100% emission at 254 nm). The contents of the ophthalmic preparations were placed in 25 ml beakers and exposed to UV light fixed horizontally in a chamber at a distance of 25 cm for a period of approximately 5 h. Samples were withdrawn at appropriate intervals for chromatographic examination and spectrometric determination.

Measurement of light intensity: The light intensity, measurement of the radiation source, was carried out, using potassium ferrioxalate actinometry (Hatchard and Parker, 1956) over a wide range of wavelengths (254–577 nm). A value of $5.56 \pm 0.12 \times 10^{18}$ quanta s^{-1} was obtained.

RESULTS AND DISCUSSION

Identification of the degradation products of sulfacetamide sodium stored in the dark: Five different brands of sulfacetamide sodium ophthalmic preparations (Table 1) were stored in the dark at 30±2°C / 65±5% RH in a stability chamber. The aliquots from each sample were withdrawn at one month interval for a period of six months. The solutions were subjected to TLC for the identification of the degradation products. Sulfacetamide sodium and its degradation products were identified by comparison of the R_f values and shape of the spots under UV light (365 and 254 nm) with those of the reference standards. It has been observed that sulfacetamide sodium is mainly hydrolyzed to sulfanilamide in the ophthalmic preparations. Similar degradation pattern has also been reported by other workers (Anderson and Maudson, 1963; Ahmad and Ahmad, 1983, Ahmad and Ahmad, 1988, Ahmad and Ahmad (1989a,b); Ahmad and Ahmad (1990); Ahmad *et al*., 1994). However, at the end of the six months storage, traces of sulfanilic acid were also observed on TLC plates, indicating that sulfanilamide is oxidized to form this product to a smaller extent. The presence of sulfanilic acid in sulfacetamide solutions has previously been reported by Phillips *et al*. (1971). TLC studies indicate that the major product of breakdown of sulfacetamide sodium is sulfanilamide, which has a considerably lower antibacterial activity than the parent compound (**S**weetman, 2009). Therefore, it is necessary to observe the formation of this compound and to check the limit of its formation to preserve the potency of sulfacetamide in commercial ophthalmic preparations.

Kinetics of degradation of sulfacetamide sodium in dark (stored samples): In order to evaluate the loss of sulfacetamide sodium in dark (i.e., on storage), the analytical data obtained on different ophthalmic preparations was subjected to kinetic treatment, using MS Excel, 2007. The data was tested for compliance with a zero, first or second-order kinetics. It was observed that the data best fit to first-order plots. The apparent first-order rate constants for the degradation of sulfacetamide sodium in different samples were determined from the slopes of the plots and are

reported in Table 2. It appears that there is a difference among these rate constants, which may be due to formulation factors, involved in the manufacture of the eye drops. The results indicate that the above mentioned factors affect the stability of sulfacetamide sodium in various ophthalmic preparations and this may lead to a change in the efficacy of the active drug on application to eyes as an antibacterial or an anti-infective agent.

Effect of pH: The kinetic data for samples 1–5 indicate that the rate constants are affected by pH. An increase in pH would lead to an increase in the rate of hydrolysis and, therefore, an increase in the values of k_{obs} (Table 2). However, in the case of sample 3 (pH 7.6), the value of k_{obs} is lower than that of sample 2 which may be due to other factors such as the viscosity of the medium and vehicle composition. A *k*–pH plot for the preparations is shown in Fig. 1, which shows a gradual increase in rate with pH in the range of 7.6–8.2. It is similar to that observed by Meakin *et al*. (1971) for the hydrolysis of sulfacetamide in this pH range.

Table 1: Ophthalmic preparations of sulfacetamide sodium used in current study.

Sample	Ophthalmic preparation	Other active ingredient	pH
1	Suspension (10%)	Prednisolone acetate (0.2%), Phenylephrine HCl (0.12%)	7.4
2	Suspension (10%)	Prednisolone acetate (0.2%), Phenylephrine HCl (0.12%)	7.5
3	Solution (10%)	Prednisolone acetate (0.25%), Phenylephrine HCl (0.12%)	7.6
4	Solution (10%)	–	8.0
5	Solution (20%)	–	8.2

Table 2: Apparent first-order rate constants (k_{obs}) for the degradation of sulfacetamide sodium in dark and light in ophthalmic preparations.

Formulation	pH	Dark		Light
		$k_{obs} \times 10^4$, day^{-1} (R^2)	$k_{obs} \times 10^7$, min^{-1}	$k_{obs} \times 10^4$, min^{-1} (R^2)
Sample 1 (10%)	7.4	6.73 (0.990)	4.67	9.24 (0.992)
Sample 2 (10%)	7.5	6.89 (0.991)	4.78	6.62 (0.990)
Sample 3 (10%)	7.6	6.63 (0.991)	4.60	8.12 (0.993)
Sample 4 (10%)	8.0	7.68 (0.991)	5.33	8.75 (0.990)
Sample 5 (20%)	8.2	7.91 (0.992)	5.49	8.05 (0.991)

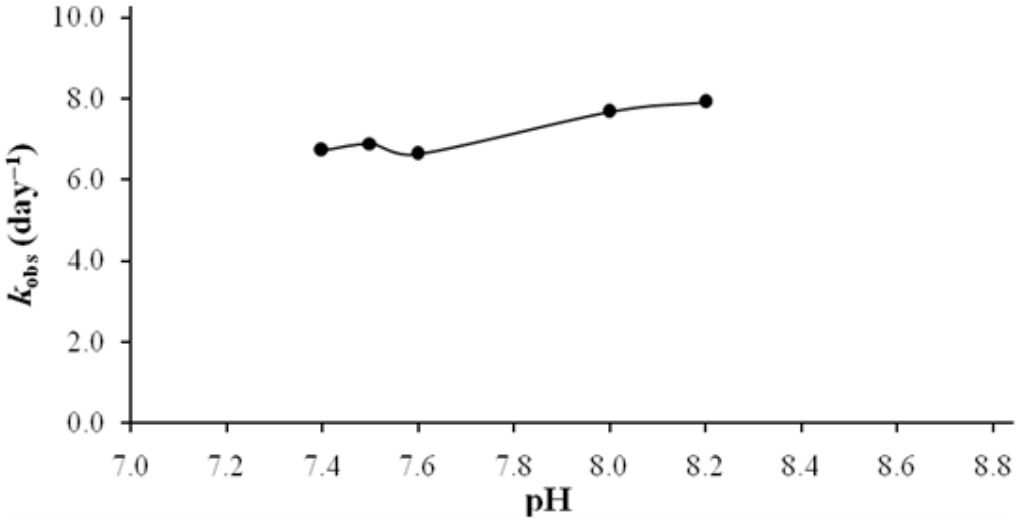

Fig. 1: A plot of k_{obs} for the degradation of sulfacetamide sodium in dark in samples 1–5 versus pH.

Effect of concentration: Samples 1–4 contain 10% sulfacetamide sodium and show the values of k_{obs} in accordance with the pH of the solutions. Sample 5 contains 20% sulfacetamide sodium and has a high rate constant than sample 1–4. This is probably due to a higher pH of the solution (i.e. 8.2) and a higher rate of hydrolysis of the drug compared with that of the

other samples (7.4–8.0). Some formulation factors may also contribute to this rate constant.

Kinetics of photodegradation of sulfacetamide sodium in ophthalmic preparations: One of the important aspects of the present study is to evaluate the kinetics of photodegradation of sulfacetamide sodium in ophthalmic preparations under controlled conditions of light intensity. The concentration versus time plots for the photodegradation of sulfacetamide sodium in different samples indicated gradual loss of sulfacetamide sodium and formation of sulfanilamide. The kinetic treatment of the analytical data showed that sulfacetamide sodium, followed first-order kinetics on photodegradation. The apparent first-order rate constants (k_{obs}) for the photodegradation of sulfacetamide sodium in various samples are reported in Table 2. The values suggest that samples containing 10% sulfacetamide are more susceptible to photodegradation as compared to those containing 20% concentration of sulfacetamide. This may be due to the fact that the same numbers of photons are available for these solutions and the 10% preparation would have a greater chance to absorb light and undergo degradation compared to that of 20% solution.

Color changes in photodegraded solutions: One of the major problems associated with the stability of sulfacetamide is its susceptibility to degradation on exposure to light and inactivation by the formation of photoproducts. Whittet (1949) observed that the eye drops of sulfacetamide turned brown on storage in colorless glass containers. The addition of H_2O_2 in the solution also caused the formation of brown color within an hour followed by the deposition of brown crystals. Anderson and Maudson (1963) studied the aerobic discoloration of sulfacetamide sodium at pH 7.0–9.0, using a fluorescent tube. The rate of discoloration was found to be affected by the pH and the unionized molecule was oxidized more rapidly than the ionized form. Clarke (1965) detected azo and azoxy derivatives in sulfacetamide sodium solution stored for one year. The solution turned deep reddish brown indicating the formation of colored oxidation product. Similar results were obtained by Clarke (1967) and Pandula *et al*. (1969). Davies *et al*. (1970) showed that these products absorb at 250 nm. A detailed study of the photodegradation of sulfacetamide solution showed the presence of hydrolytic (sulfanilamide) and oxidation (azo and azoxy derivatives) products on degradation (Ahmad and Ahmad, 1981).

All ophthalmic preparations (10–20%) subjected to photodegradation showed the development of a brown color after ~5 h of UV irradiation. TLC indicated the presence of azobenzene-4,4′-disulfonamide in the photolyzed solutions. However, no peak could be detected spectrophotometrically in the visible region, which could be due to the presence of the parent compound in a large excess and azobenzene-4,4′-disulfonamide (λ_{max} 320 nm) (Ahmad and Ahmad, 1989b) in minute amount. Furthermore, the high dilutions would have made this product negligible in the samples. Therefore, the photodegraded solutions could not be analyzed for azo compound on the basis of a three component spectrometric assay.

Comparison of dark and light reactions: A comparison of the values of k_{obs} for the photodegradation of sulfacetamide sodium with those of the samples, stored in the dark, shows that the rate constants for photodegradation ($6.62–9.24\times10^{-4}$ min^{-1}) are about 1500 times higher than those of the degradation in dark ($4.60–5.49\times10^{-7}$ min^{-1}). This appears to be due to the fact that photochemical reactions are involved in the formation and participation of radicals to initiate the process which are very fast as compared to the chemical reactions occurring in the dark. In the case of sulfacetamide sodium (pH 7–8), the hydrolytic degradation in ophthalmic preparations is very slow and, therefore, the rate constants are much smaller than those of the photodegradation reactions. These data indicate that the photodegradation reaction is more effective in causing the loss of potency of sulfacetamide sodium and proper protection is necessary to minimize this loss.

CONCLUSION

The present study has demonstrated that the ophthalmic preparations of sulfacetamide sodium are susceptible to degradation in dark as well as on exposure to UV light. The formulations undergo degradation to form sulfanilamide in the dark and sulfanilamide and azobenzene-4,4′-disulfonamide on irradiation to UV light. These degradation products have been identified by thin-layer chromatography and spectral variations of degraded solutions.

The loss of the drug in 10% ophthalmic preparations in dark is about 10–12% and about 22% in 20% preparations on storage for 6 months. On the contrary, the photodegraded samples (10%) lose about 10% concentration in 100–140 min and those at the higher concentration (20%) in about 60 min. The chemical and photodegradation follows apparent first-order kinetics. The concentration, pH, viscosity, vehicle and inactive ingredients (e.g., antioxidants, stabilizers and preservatives) appear to influence the rate of degradation of sulfacetamide sodium in ophthalmic preparations.

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