CHAPTER IV

DISCUSSION

Various experiments were done to study the most suitable methods for evaluation of the color formation and for analysing sulfacetamide in sulfacetamide sodium eye solution.

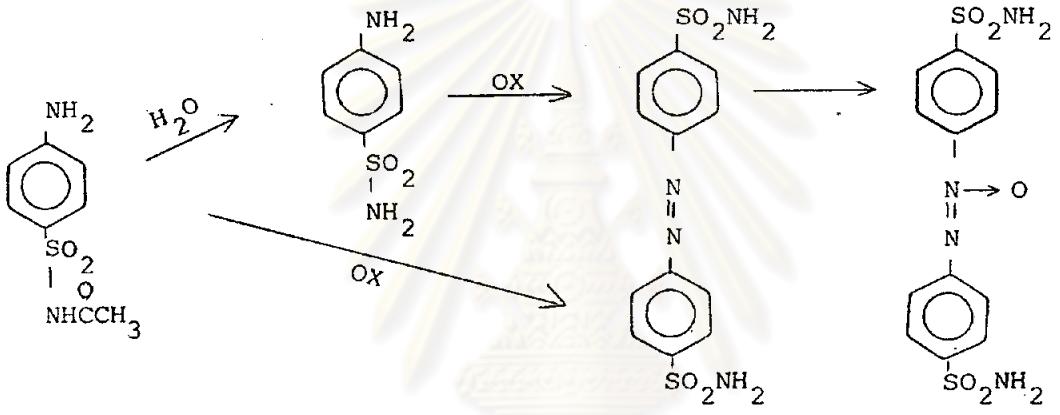
From the results of experiment in this study, it is found that sulfacetamide sodium developed color from its colorless solution to yellow through reddish brown color depending upon the time of exposure to both natural sunlight and artificial daylight light (fluoresent lamp, 40 W.). This is in agreement with that previously observed (33). The artificial daylight light is chosen to be used throughout this study because it is easier to control the intensity and time of exposure while the natural sunlight varies at all times. It is found that after exposure to light the absorption spectrum of sulfacetamide sodium solution show an absorption peak at 450 nm. At this wavelength, there is no interference from other ingredients used in various experiments. The development of absorbance peak at 450 nm is in good correlation with color formation by comparing with standard caramel solutions.

The degradation of sulfacetamide sodium solution is quite complicated. The formation of sulfanilamide due to the hydrolysis is well-known, but the color formation due to the exposure to light is still not well established. It is most likely to occur through various oxidation routes as studied by Clarke (15) and Pandula (16). The series of reactions were thought to be:

(a) The hydrolysis of sulfacetamide to sulfanilamide, and subsequent oxidation to azobenzene-4, 4'-disulfonamide and/or azoxybenzene

(b) Direct oxidation of sulfacetamide to azobenzene-4, 4'-di (N-actyl sulfonamide), and/or azoxybenzene-4, 4'-di (N-acetyl sulfonamide)

(c) Reaction (a) and (b) occuring together.



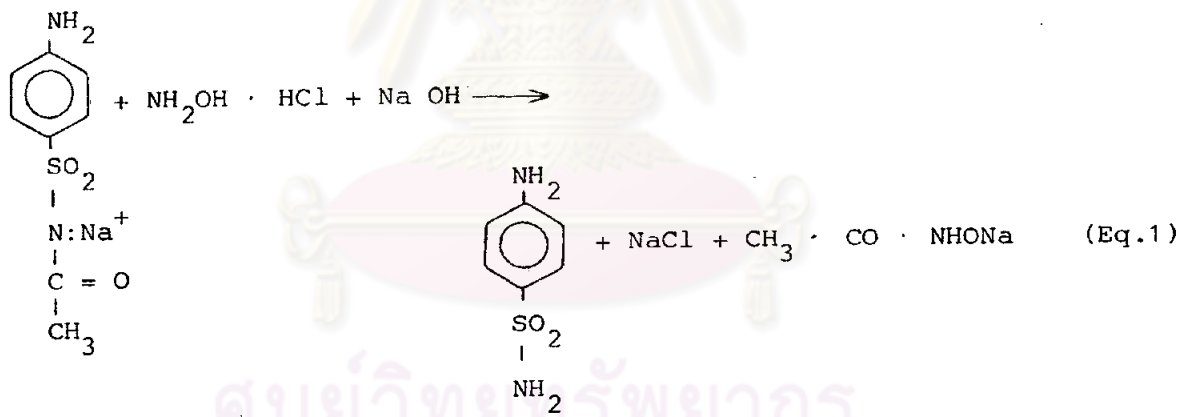
(d) Other oxidation products are also present, especially in the solution of sulfacetamide sodium which has been stored for many months.

The absorption peak at 450 nm could be one of the oxidation products proposed in reaction (c).

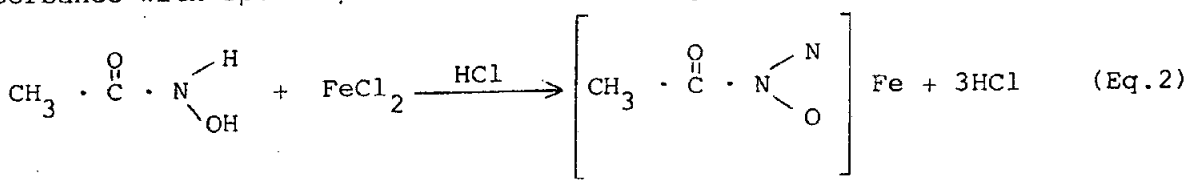
Therefore, from various experiments done in this study, it is clearly shown that the absorbance at 450 nm can be used to follow the changes of color of the solution quite accurately, without any interference from other ingredients used.

The analytical procedure for degradation products,one of which is sulfanilamide is not used in assaying the degradation of sulfacetamide

solution. Official method in U.S.P. or BP to check the amount of sulfacetamide sodium is based on the diazotization of the primary amino group attached to the aromatic ring. This functional group is present in both sulfanilamide and sulfacetamide sodium so this method of analysis can not be used to differentiate between the two sulfonamides. Therefore quantitative analysis of sulfacetamide sodium solutions in the presence of degradation products, sulfanilamide, is chosen from the method developed by Schleider et al. (31). Briefly hydroxylamine hydrochloride is used to react with carboxylic acid derivatives in an alkaline media. Carboxylic acid derivative can be converted to corresponding hydroxylamic acid salt. (Eq.1)



The acetyldroxamic acid salt produced could then react with ferric chloride in acid medium at optimum temperature and duration to produce the colored ferric hydroxamate (Eq.2) which can be determined by measuring the absorbance with spectrophotometer at wavelength of 540 nm.



This method is being employed in this experiment to determine sulfacetamide sodium in solutions prepared (table 2). The potency of solutions changes slightly and is still within the limits of the BPC, 95-105%. Therefore, the preparations will be considered to be of standard quality in this respect. Degree of discoloration appeared to be no correlation between the degradation products content and the intensity of color of the solution.

Effects of various parameters on the rate of color formation of sulfacetamide sodium solution were studied carefully. It is indicated that sulfacetamide is oxidized faster in acidic pH than in alkaline pH. The color formed in the 10% sulfacetamide sodium solution is minimal. This is due to the pH of the solution is above 9.0. The formation of color is faster in less concentrated solutions which have lower pH respectively. In controlling pH of the solution, buffer is oftenly used. However, the ophthalmic phosphate buffer tested in this study shows a catalytic effect on the color formation. The higher buffer concentration used will cause faster color formation. Therefore it may not be worthwhile to use phosphate buffer in this case. Since the pH of sulfacetamide sodium solution is too high to be used as eye drop. The highest acceptable pH would be 8.0.

In the studies of effect of various concentration of additives, antioxidants and chelating agent, it is found that sodium metabisulfite, a widely used antioxidant in eye drop can retard the color formation at a high concentration. The effect is good only in a short duration of time after the exposure to light. It has been used mostly in the

concentration about 0.1-0.2%. The result from this study indicates that the amount used must be about 0.2% or higher in order to be able to prevent the color formation of sulfacetamide sodium solution.

In the case of sodium thiosulfate, the results show that this antioxidant is much more effective than sodium metabisulfite. In the same concentration range used as in the case of sodium metabisulfite, this antioxidant can significantly lower the color formation of the solution, even at the lowest concentration used, 0.1%. Anyhow, the pH of the solution is higher than when sodium metabisulfite is used. The better effect of sodium thiosulfate is proved not to be due to the higher pH of the solution. It is clearly shown that even at the same pH (buffered at pH 7.4), sodium thiosulfate has much higher efficiency in retardation of the color formation.

It is quite well documented that the degradation by oxidation could be catalyzed by the present of small amount of metals. A chelating agent is often used to prevent this catalytic effect. Disodium EDTA is used in this study. However, the use of disodium EDTA alone can not retard the color formation. The color formation is less when this chelating agent is used in combination with antioxidants. The effect observed when it is used with sodium thiosulfate is not much different from the use of sodium thiosulfate alone. The concentrations range of disodium EDTA used,0.01-0.1% show slight improvement in the prevention of color formation. However the use of disodium EDTA will lower the pH of 10% sulfacetamide sodium solution from 9.1 to about 8.0 which is acceptable for eye drop. The overall effect of antioxidants and chelating agent used can be stated

that the use of sodium thiosulfate in combination with disodium EDTA is better than the use of sodium metabisulfite with disodium EDTA.

From various formulations, it is clearly shown that the best formular for 10% sulfacetamide sodium solution is the one that uses 0.1% sodium thiosulfate as antioxidant and 0.05% disodium EDTA. This solution has pH of 8.0. The color formation is very much retarded further by filling the solution in amber glass ampules.