CHAPTER I

INTRODUCTION

Drugs are instilled into the eyes for anesthetic, diagnostic, mydriatic, miotic, anti-inflammatory, or anti-infective purposes. Most frequently aqueous solution are employed; however, nonaqueous solutions, suspensions, and ophthalmic ointments are also commonly used.

Ophthalmic solutions are sterile, usually isotonic and buffered solutions, free from foreign particles, and intended for instillation into the eyes. They are also called eye drops or collyria.

Eye lotions or eye washes (collyria) are actually ophthalmic solutions, but they are usually soothing solutions containing such drugs as boric acid, borax, sodium chloride, or zinc sulfate. Ophthalmic solutions are applied in drop form, but eye lotions are instilled with an eye cup. Thus, the eyes are literally washed with a sufficient quantity of the mild solution.

Ophthalmic suspensions are sterile aqueous suspensions of very finely divided particle of drugs and contain a suitable bacteriostatic agent, and may contain a suitable suspending agent to retard sedimentation. They are used in drop form in the manner similar to ophthalmic solutions.

Ophthalmic Ointments are sterile preparation containing a medicinal agent incorporated into a suitable ointment base either as a solution or as a micronized powder so that the finished ointment is free from large particle. The ointment base must not irritate the eye, must

permit diffusion of the drug throughout the secretion bathing the eye, and must retain the activity of the drug for a reasonable period under proper storage conditions.

Contact lens solutions are sterile aqueous solution composed of substances intended to supplement the lacrimal fluid of the eye of persons who wear contact lens, which help minimize pressure of the lens against the eyes.

Considerations in Preparing Ophthalmic Medication (1)

The professional compounding of ophthalmic preparations employed for these purposes requires great care and skill, and special attention to the technique in order to prevent contamination. Eye solutions should be prepared with at least as much care as intravenous solutions. Eye drops are often instilled into eyes traumatized by accident or surgery, and they are then potentially even more dangerous than intravenous injections.

The most important factors to consider when preparing an ophthalmic solution are:-

1. Isotonicity
2. Buffering (pH)
3. Active ingredients
4. Preservatives
5. Viscosity-producing and other additives
6. Stability
7. Filtration

8. Sterility

9. Packaging

Characteristics of Lacrimal Fulid (2):

Lacrimal fluid is a secretory product of the lacrimal gland and not a filtrate of blood. It contains lysozyme, an enzyme has been postulated to confer protective action. The fluid is rich in total protein, approximately 0.7% W/V which contributes significantly to the acid base buffer characteristics of the tears, and must be saturated with CO_2 in order to bring the pH to the physiological pH of 7.4. The pH of lacrimal fluid is at least 7.4 and may possibly be more alkaline because as a single drop of lacrimal fluid is exposed to the air, CO_2 will escape and the pH will rise to over 8 and then slowly to approximately 9.

The lacrimal fluids is iso-osmotic with 0.9% sodium chloride solution. However the eyes can in fact tolerate a considerable range of tonicity before any pain or discomfort is suffered or any corneal epithelial damage is sustained. They can tolerate sodium chloride in a concentrations range of 0.5 to 2.0%. Eventhough sodium chloride solutions of concentration up to 10% are unlikely to cause any damage to the eyes by virtue of their hypertonic character.

ISOTONICITY:

Aqueous solutions intended for parenteral injection or applied to the delicate membranes of the body should be adjusted to approximately the same osmotic pressure as the body fluid with which they come into contact.

Two solutions which have the same osmotic pressure are defined as iso-osmotic. The term "isotonic" is more widely used in pharmacy. Isotonic solutions cause no swelling or contraction of the tissue with which they come into contact and produce no discomfort when instilled into the eyes. Body fluids, including blood and lacrimal fluid have been found to be isotonic with 0.9% W/V sodium chloride solution. Solutions with a lower osmotic pressure than body fluid or 0.9% sodium chloride solution are commonly refered to as "hypotonic", where as solution having a greater osmotic pressure are termed "hypertonic".

If an ophthalmic solution is iso-osmotic with the lacrimal fluid, the irritant action due to osmosis is avoided. So far, the sensitivity of the eyes to the variation in osmotic pressure is much lower than its sensitivity to pH and the nature of the medicament and preservative. Ophthalmic solutions with osmotically equivalent to sodium chloride solutions ranging in strength from 0.5 to 2% are generally well tolerated, neither pain is suffered, nor tissue changes detected. The BPC ignores osmotic pressure in most of its eye drop formulations (2).

BUFFERING (pH):

Buffer may be used in an ophthalmic solution for one or all of the following reasons;

(1) to reduce discomfort to the patient

(2) to ensure drug stability, and

(3) to control the therapeutic activity of the drug substance.

Lacrimal fluids have a pH of about 7.4. The buffering power (2,3) (due to carbonic acid, weak organic acids and protein) is enough to

neutralize quickly the pH of unbuffered solutions over a wide range (3.5 to 10.5) provided the volume is small, as is usually the case with eye drops, of which the normal volume instilled is only 1 or 2 drops (0.05-0.1 ml.). However, consideration in buffering solutions depends on the concentrated solutions of very acidic drugs, such as adrenaline acid tartrate and pilocarpine hydrochloride. Sometimes, a compromise pH is generally selected for a solution and maintained by buffer to permit the greatest activity while maintaining stability.

ACTIVE INGREDIENTS:

The active ingredients, as well as additives such as preservatives, antioxidants, and buffers, used to prepare ophthalmic medications must be of the highest purity available, and be stored under proper conditions.

PRESERVATIVES:

In order to prevent the growth of micro-organisms, accidentally introduced during use, eye drops which are dispensed in multi-dose containers must contain a suitable preservative. The properties of an ideal preservative are; rapidly effective against a wide range of organisms, particularly "Pseudomonas aeruginosa", non-irritant to the eye, non toxic, cause no pain or stinging, compatible with the medicaments used in eye preparations and eye drop containers and closures, and stable during sterilisation and storage.

VISCOSITY-PRODUCING AND OTHER ADDITIVES:

In the preparation of ophthalmic solutions, vicosity-producing or other thickening agents are frequently added to increase the viscosity

and thereby aid in holding the drug in contact with the tissue so as to enhance the therapeutic effectiveness. They also serve to replace deficient tear secretion of aged persons and sometime serve as a lubricant in special situation. Generally, methylcellulose 4000 centipoise viscosity is used in 0.5 to 1.0% concentration.

Antioxidants are permissible in appropriate concentration in ophthalmic solutions to provide protection from oxidation. In contrast to antioxidants, reducing agents are effective agents and act by being oxidized in preference to the drug they are protecting. The minimum concentration that gives the disired protective effect should be chosen.

The reducing agents most commonly used in ophthalmic solutions are sodium metabisulphite, sodium bisulphite and sodium thiosulphate, in some commercial products (4).

Sequestering agents are used, either alone or with a reducing agent to limit decomposition in certain eye drop. They have the ability to greatly enhance antioxidant efficiency. The most popular compound, disodium edetate forms complexes with di and tri valent matals. It is harmless to the eyes and compatible with most common eye drop medicaments.

STABILITY:

The pharmacist must be consciously aware of the importance of stability in ophthalmic preparations. Since eye drops are not usually freshly prepared,they must be formulated so that the active drug has a reasonable shelf life. Several factors that affect the stability may increase the rate of deterioration, for example, hydrolysis, oxidation,

pH, light, heat, types of containers and closures and methods of preparation.

FILTRATION:

All ophthalmic solutions must be filtered to ensure that all particulate matter is removed. Further, some ophthalmic drugs are unstable at autoclaving condition, bacterial filtration must be used to obtain a sterile solution and remove particulate matter.

STERILITY:

Ophthalmic preparations should be sterile. When they are prepared in multidose containers the vehicle employed should be bactericidal and fungicidal to minimize the risk of contamination during use. In order to ensure sterility of the final product, the solution should be prepared under aseptic conditions.

PACKING:

An important factor in ophthalmic preparations is proper packaging and closing. An ophthalmic package must protect the contents from light if the drug is light-sensitive.

For domiciliary use and for intact eyes in hospital practice, eye drops are dispensed in multidose containers, frequently not more than 10 ml. The conventional type of eye drop bottle is made of glass and is closed by a screw-cap through which the eye dropper and teat are inserted. The BPC specifies that such containers should comply with British Standard 1679: Part 5: 1965,. This requires that the bottle is amber coloured, vertically ribbed and made of neutral glass or soda

glass which has been surface treated to limit the amount of alkali released into aqueous solutions (5).

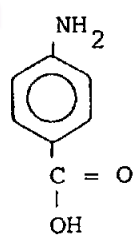
The BPC also permits the use of suitable plastics containers for eye drops. Such containers must be compatible with the preparation and not release undersirable materials (e.g. plasticizers) into the solution.

Whilst eye drops in multidose containers are prepared with a preservative there is always the danger of contamination with resistant organisms or the accumulation of dead bacterial cells and their contents. Therefore, in an attempt to minimize this the BPC has made recommendations as to how long a multidose container should remain in use after opening. For home use a period of not longer than four weeks is recommended unless there is other special storage recommendation. For hospital wards a separate container should be provided for each patient. They should be discarded not later than one week after first opening.

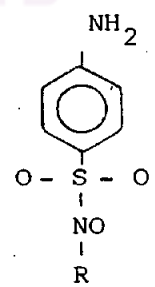
THE SULPHONAMIDES:

Sulphonamides are synthetic compounds which have a structural similarity to para-aminobenzoic acid (PABA).

PABA



Sulphonamide

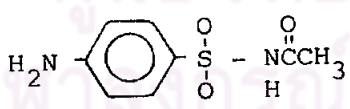


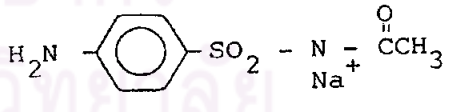
Sulphonamides are relatively broad spectrum, acting against Gram-positive as well as Gram-negative bacteria. In the concentrations used are usually bacteriostatic (that is, they inhibit growth and multiplication), in higher concentrations they may be bactericidal.

Sulphonamides are weak acids, they will form salts with bases. The water-solubility of salt forms increases over that of the free sulphonamides.

Generally, the free sulphonamides are relatively insoluble in water, while their sodium salt are very soluble. The high pH of the sodium salt of sulfa drugs, with the exception of sodium sulfacetamide, causes them to be damaging to tissues, results in incompatibilities with acidic substances and brings about decomposition of most vasoconstrictors (6).

Sulfacetamide is N'-acetyl sulfanilamide or N-sulfamilylacetamide





Sulfacetamide

Sulfacetamide sodium

This compound is soluble in water (1:62.5) at 37°C, and very soluble in hot water. Its water solution is acidic. It has a pKa of 5.4. The sodium salt of sulfacetamide is obtained as the monohydrate and is a white, odorless, bitter, crystalline powder which is water soluble, 1 in 1.5 of water. The solution is less alkaline than solutions of most other sulphonamides. A solution of 3.85% sulfacetamide sodium is iso-osmotic with serum. A 5% solution in water has a pH of 8 to 9.5. A mixture of sulfacetamide sodium and 1% sulfacetamide gives a solution in water which has a pH of about 7.4. The pH of 10% (W/V) aqueous solution is 9.0 and the pH of 30% aqueous solution is 7.4 (glass electrode). Sulfacetamide sodium solution discolor on exposure to air and light. Sodium edetate alone, sodium thiosulfate, or ascorbic acid did not retard discoloration. Metabisulfite alone retards discoloration until the bisulfite is oxidized, then the solution discolor even more rapidly. Sodium edetate(0.1%)and sodium metabisulfite(0.1%) was proved to be an effective combination. All solutions was adjusted to pH 8 to 9.9(7). Because the sodium salt is highly soluble at the physiologic pH of 7.4, it is especially suited as a solution for repeated topical application in the local management of ophthalmic infections susceptible to sulphonamide therepy.

Sulfacetamide sodium is the sulphonamide most widely used by opthalmologists, although there are antibiotics which possess either bacteriostatic or bactericidal activity. The main danger in improper use of antibiotics is the production of strains of bacteria which are resistant to the action of antibiotics. Once resistance has developed there is the problem of finding a suitable alternative treatment, and in extreme cases no satisfactory alternative may be found.

Sulfacetamide sodium is used mainly by local application in infection or injury of the eyes, available in eye drops and ointment. The ointment causes less discomfort than the drops and remain longer in the eyes. Sulfacetamide eye drops in concentration of 10% may be used prophylactically after contact lens work, removal of a foreign body or in other situations in which corneal abrasion are likely to have occured. Even the 10% drops are hypertonic and may cause stinging. Although drops of a higher concentration are available these are usually reserved for the treatment of corneal, conjunctival and lid infection. The use of these drops would be therapeutic rather than prophylactic. Sulfacetamide drops are available in concentration of 10, 20 and 30% in multidose containers (8).

Sulfacetamide drops 10% are official in many pharmacopeias, such as USP, BP, BPC. It is also one of 71 drugs listed for household remedy in Thailand (9).

Sulfacetamide Sodium Ophthalmic Solution (USP) is a sterile solution of sulfacetamide sodium. It may contain suitable buffers, stabilizers, and antimicrobial agents. It should be stored in a cool place in airtight containers, and protect from light.

Sulfacetamide Sodium Eye drops (BP) is a sterile solution of sulfacetamide sodium in water. When intended for use on more than one occasion they contain the equivalent of not more than 0.1% of sulphur dioxide and phenylmercuric acetate or nitrate(0.002%)or thiomersal(0.01%) and should not be used later than 4 weeks after first opening of the container. The solution has pH 6.6 to 8.6. The amount of air in the final containers should be kept to a minimum.

Sulfacetamide Eye Drops (BPC) is a sterile solution containing up to 30% of sulfacetamide sodium with suitable preservatives and stabilizing agents in freshly boiled and cooled water. A suitable solution may contain (0.1%) sodium metabisulphite, 0.002% phenylmercuric acetate or nitrate or (0.01%) thiomersal and disodium edetate, 0.02% and 0.05% respectively, in solution containing sulfacetamide sodium at 10 and 30%. It should be stored at room temperature and protected from light.

The formulation of sulfacetamide eye drops for household remedy in Thailand is:

Sulfacetamide sodium	10.000	g.
Sodium metabisulphite	0.100	g.
E D T A	0.050	g.
Phenylmercuric nitrate	0.002	g.
Distilled water maked up to	100.000	ml.

STATE OF PROBLEM:

Whittet (10) demonstrated that aqueous solutions of sulfacetamide sodium decomposed more rapidly in clear glass bottles than in brown glass bottles. It was suggested that the discoloration might be caused by atmospheric oxidation and certain intensities of light after keeping on prolonged storage. It degraded to form compounds which impart yellow brown color to the solution.

Fletcher and Norton (11) observed that heating solutions of sulfacetamide sodium resulted in hydrolysis with the formation of sulfanilamide.

Several workers have shown that other sulphonamides undergo oxidative decomposition to form colored solutions. Seikel (12) reported that sulfanilamide could be oxidised with potassium ferricyanide to azobenzene-4, 4'-disulphonamide and with hydrogen peroxide and glacial acetic acid to azoxybenzene-4, 4'-disulphonamide. Kouje and Tsuji (13) obtained similar results. Levitan (14) reported the oxidation of sulfanilamide to p-hydroxyamine benzene sulphonamide, p-nitrobenzene sulphonamide and azoxybenzene-4, 4'-disulphonamide.

Clarke (15) and Pandula, et al. (16) found yellowish brown to deep reddish-brown coloration which occurred in the solution of sulfacetamide sodium due to the decomposition on storage by hydrolysis and oxidation.

Anderson (17) has shown that the rate of hydrolysis of sulfacetamide was independent of pH in the range of 7.15 to 8.9 and a more acidic pH caused increased discoloration. The hydrolysis reaction rate was first order. Heating in an autoclave at 120°C for 20 minutes or at 115°C for 30 minutes resulted in a 1% loss of potency. Autoclave is the mothod of choice.

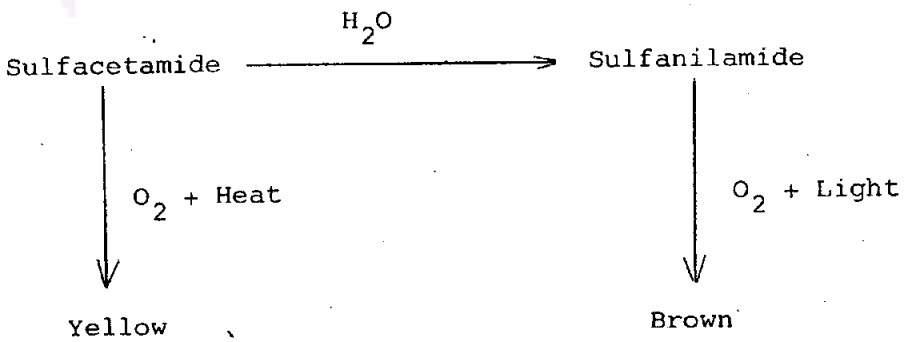
Forse (18) worked on the problem of formulating a 30% solution of sulfacetamide sodium which would neither darken nor crystalize during at least 1 year storage at room temperature in an amber glass dropper bottle containing an appreciable proportion of air. Crystallization was not normally a risk if the solution was not heated, exposed to light, or refrigerated. The inclusion of sodium metabisulphite did not affect crystallization. Unless the equivalent of 0.5% of sodium metabisulphite was added, the solutions could however discolor. Sodium thiosulphate 0.1%

was a promissing stabilizer, but sodium sulphite was less effective.

Clarke (19) has studied on the crystals of sulphanilamide deposited in 30% solution of sulfacetamide sodium after steaming at 98°-100°C for 1 or 2 hours followed by 7 weeks storage. Crystallization could be minimised by buffering the solution to pH 9 to 9.5, though discoloration was worse at pH 8.6 than at pH 7.2. Furthermore, the rate of discoloration of solution increased with increasing concentration of sulfanilamide. Though sulfacetamide hydrolysis was independent of pH at 7.5 to 8.9, sulfanilamide was less soluble at pH 7.15 and was therefore more liable to crystallise.

Mital and Gupta found that adding 0.1% of disodium edetate to a 10% solution of sulfacetamide sodium at pH 8.8 appeared to minimise the development of color changes on heating or storage.

Davies, et al. (20) have investigated the effect of heat and light stresses on the degradation of sulfacetamide. Sodium metabisulphite accelerated the hydrolytic degradation of sulfacetamide to sulphanilamide, whereas disodium edetate does not change the rate. In solution of pH 7, in the presence and absence of the antioxidants, sodium metabisulphite and disodium edetate, it was shown that in the presence of oxygen, heat and light led to different products, their scheme is as follow:



Though these colored products have not been identified, they have disagreed with the interpretation of the oxidative decomposition as shown by Clarke (15). In the absence of oxygen, no color formation is observed when sulfacetamide sodium solution exposed to heat or light.

Meakin, et al. (21) have investigated the effect of heat, pH and some buffer materials on the hydrolytic degradation of sulfacetamide in aqueous solution. The sole breakdown product is sulfanilamide. The reaction was essentially independent of pH over the range 5 to 11, but was subject to catalysis by buffer constituents.

Devi, et al. (22) have experimented for detection and estimation of sulfanilamide in sulfacetamide eye drop which developed yellowish brown coloration on exposure to heat and light. The content of sulfanilamide, an undersirable product, formed by hydrolysis of sulfacetamide has been found to lie within the limits of the BPC, not exceed 1.5% W/V (23). Degree of discoloration in sulfacetamide solution appeared to be no correlation between the sulfanilamide content and the intensity of brownish coloration of the solution.

Raisa,(24) has demonstrated that the optimal pH for the stability of the aqueous solutions of sulfacetamide sodium in the presence of various buffer systems with regard to hydrolytic degradation as well as oxidation on the color formation is 8 to 8.5.

Pawlaczyk,et al. (25) was interested in photochemistry of photodynamic compounds on photolysis of sulfacetamide and its sodium salt in aqueous solution with monochromatic radiation of 254 nm, photolysis courses were followed by paper chromatography of the solution. They

found 18 decomposition products in the sulfacetamide solution and 16 products in the sodium salt solution. Kinetic of formation of sulfanilamide, sulphanilic acid and sulphur dioxide were measured.

Hydrolysis is not a serious problem in sulfacetamide solution at room temperature. Oxidative decomposition under light stress can be prevented by removing oxygen from solution and storing in sealed ampules. Antioxidants are often added to sulfacetamide solutions. As noted earlier, sodium metabisulphite, as an antioxidant in BPC and household remedy eye drop of sulfacetamide solution, added to reduce color development, acts as a catalyst in the hydrolytic reaction; moreover, sodium metabisulphite is not very effective in preventing color formation (26).

The photolytic degradation can be an important limiting factor in the stability of pharmaceuticals ,colored glass containers are most commonly used to protect light sensitive formulation. The photodegradation of sulfacetamide solutions may be inhibited by an antioxidant such as sodium thiosulfate or metabisulfite (27).

On those problems, some commercial preparations of sulfacetamide sodium ophthalmic solution - Albucid (Nicolas, UK), Sodium Sulamyd Ophthalmic Solution (Schering) utilize phosphate buffers to maintain the pH at about 7.4 and sodium thiosulfate is employed as a stabilizer to prevent the darkening of the solution (28).

PURPOSE OF STUDY:

The purposes of this investigation are (a) to study the effect of antioxidants in color formation of sulfacetamide sodium eye drop

under light stress in order to choose the proper antioxidants (b) to evaluate the effect of using various concentrations of antioxidants, and (c) to determine the quantity of additives which give the maximal protection of photodegradation of sulfacetamide sodium eye drop.

The results obtained from this investigation should bring about a more stable sulfacetamide sodium eye drop and improve aqueous formulation of this photosensitive pharmaceutical product.

Antioxidants (29)

The most commonly empoyed water soluble antioxidants, used in ophthalmic solution are sulfurous acid salts.

1. Sodium bisulfite

   Solubility: Soluble in water produces solution of acidic pH.

   Concentration: 0.05% - 1.0%

   Stability: Bisulfite is more stable and effective as an antioxidant in solutions at pH of 1 to 5.

2. Sodium metabisulfite

   Solubility: Soluble in water produces solution of acidic pH.

   Concentration: 0.025 - 0.1%

   Stability: Metabisulfite is most stable and effective in solutions at low pH.

3. Sodium sulfite

   Solubility: Soluble in water produces solution of pH 9.

   Concentration: 0.01% - 0.2%

   Stability: Sulfite is more stable and effective as an antioxidant in solutions at pH of 7 to 10.

4. Sodium formaldehyde sulfoxylate

   Solubility: Soluble in water produces solution of pH 9 to 11.

   Concentration: 0.005% - 0.15%

   Stability: Store below 40°C and protected from light.

5. Sodium thiosulfate

   Solubility: Soluble in water produces solution of pH 6.5 to 8.0.

   Concentration: 0.1% - 0.5%

   Stability: Unstable at acidic pH.

From the antioxidants listed above, sodium thiosulfate is suitable to be use in sulfacetamide sodium eye drop because of its solution has a pH between 6.5-8 and has been used in some commercial sulfacetamide sodium eye drops.