A PHARMACEUTICAL SERVICE TO OPHTHALMOLOGY PATIENTS: STUDIES ON CEFUROXIME PREPARATIONS

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by

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The Pharmaceutical Department at the Birmingham and Midland Eye Hospital frequently receives requests for information about the dosage and preparation of periocular and intraocular injections and the preparation of extemporaneously prepared eye drops. The major national reference source for both subjects is the Moorfields Eye Hospital Pharmacopoeia. Apart from this information source reference must be made to original papers on the subject.

The first part of this project is concerned with an investigation into the practices of other hospitals treating ophthalmic patients regarding ophthalmic injections and extemporaneously prepared eye drops. A questionnaire was distributed to 110 hospitals with dedicated ophthalmic beds. The results showed a close parallel between the preparation of extemporaneous antimicrobial eye drops and the use of ophthalmic injections of the same antibiotic. The general response received to the questionnaires indicated that the provision of information on the subject of ophthalmic injections was desirable and necessary, and a booklet about these injections has been prepared.

It was evident from the responses received to the questionnaires that formulation and stability information was available for those penicillin eye drops which are most frequently prepared. However the use of cephalosporin eye drops is becoming increasingly important with the emergence of methicillin-resistant micro-organisms. No formulation or stability work has been published about the preparation of cefuroxime eye drops, the most widely reported preparation in this group. The second part of this project investigates the formulation and stability of cefuroxime eye drops, when prepared in a number of artificial tear solutions, and concludes that the preparation of Cefuroxime 5% eye drops in Sno Tears is the most appropriate formulation.

Keywords: Cefuroxime, Periocular, Intraocular
Eye drops, Formulation.

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Dedication

To Derek and Daniel

CONTENTS

LIST OF TABLES

LIST OF FIGURES

PART 1

THE USE OF OPHTHALMIC INJECTIONS AND EXTEMPORANEOUSLY PREPARED EYE DROPS IN THE UK

1.1 THE STRUCTURE AND FUNCTION OF THE EYE

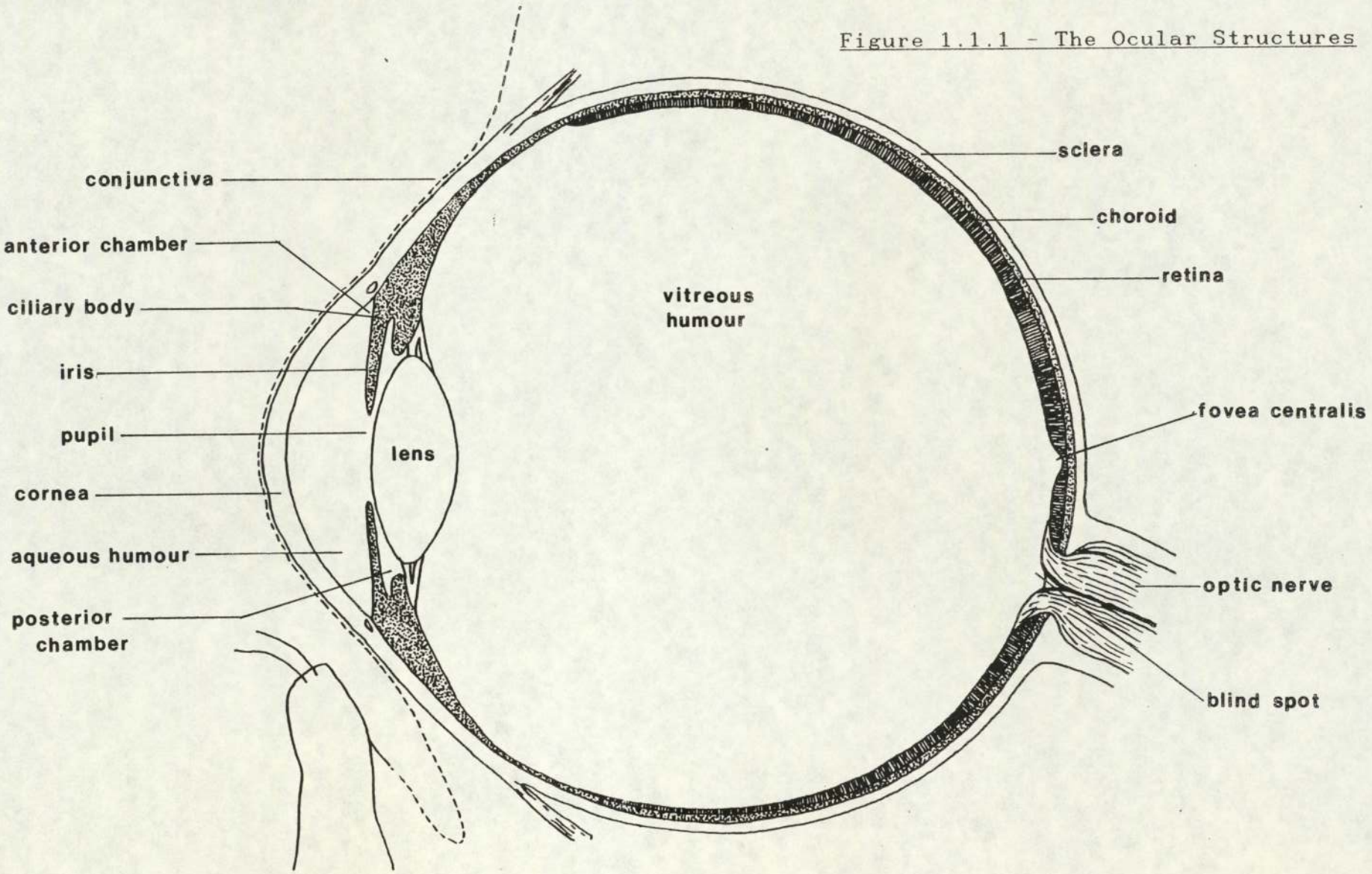
The eye provides information to the brain about the shape, size, colour and position of objects in the environment. All parts of the eye work together to fulfil this aim. The human eye is a hollow sphere of about 2.5cm diameter, which lies, suspended in a bed of fat, in the anterior part of the bony orbit of the skull. The eyeball is protected by this orbit and by two folds of skin; the eyelids, which can cover the eyeball and contain secretory glands responsible for the production of tears. Six muscles are involved in the movement of the eyeball within the orbit. These are the superior, inferior, medial and lateral rectus muscles, and the superior and inferior oblique muscles. The globe is made up of three coats; the outer fibrous coat consisting of the sclera and cornea, the middle vascular layer, known as the uvea, made up of the choroid, ciliary body and iris and the inner nervous layer, the retina. The lens lies behind the iris and is attached by suspensory ligaments to the ciliary body. The chamber between the cornea and iris is known as the anterior chamber, while that between the iris and lens is the posterior chamber. Both are filled with aqueous humour. Behind the lens is the vitreous chamber, filled with a viscous substance, which is known as vitreous humour. [1,2]

1.1.1 The Ocular Structures

1. The Sclera

This tough white fibrous coating covers the posterior 80% of the eyeball. It is continuous with the cornea at the front of the eye. There is an opening at the back of the sclera

Figure 1.1.1 - The Ocular Structures



through which passes the optic nerve fibres, arteries and veins.

2. The Cornea

The cornea is a transparent tissue at the front of the eye continuous with the sclera. It comprises five layers.

a) Epithelium - 5 or 6 layers of cells which are constantly being replaced in a similar way to the epithelium of the skin. This layer is continuous with the conjunctiva.

b) Bowman's Membrane - lies on the inside of the epithelium, between it and the corneal stroma. It cannot regenerate and if damaged, corneal scarring occurs.

c) Corneal Stroma - the thickest part of the cornea, consisting of broad bands of fibrils which run parallel to the surface of the cornea. The regular structure of the stroma gives transparency to the cornea.

d) Descemet's Membrane - this membrane between the stroma and endothelium can regenerate if damaged.

e) Endothelium - a single layer of cells, which cannot regenerate, forming the inner layer of the cornea.

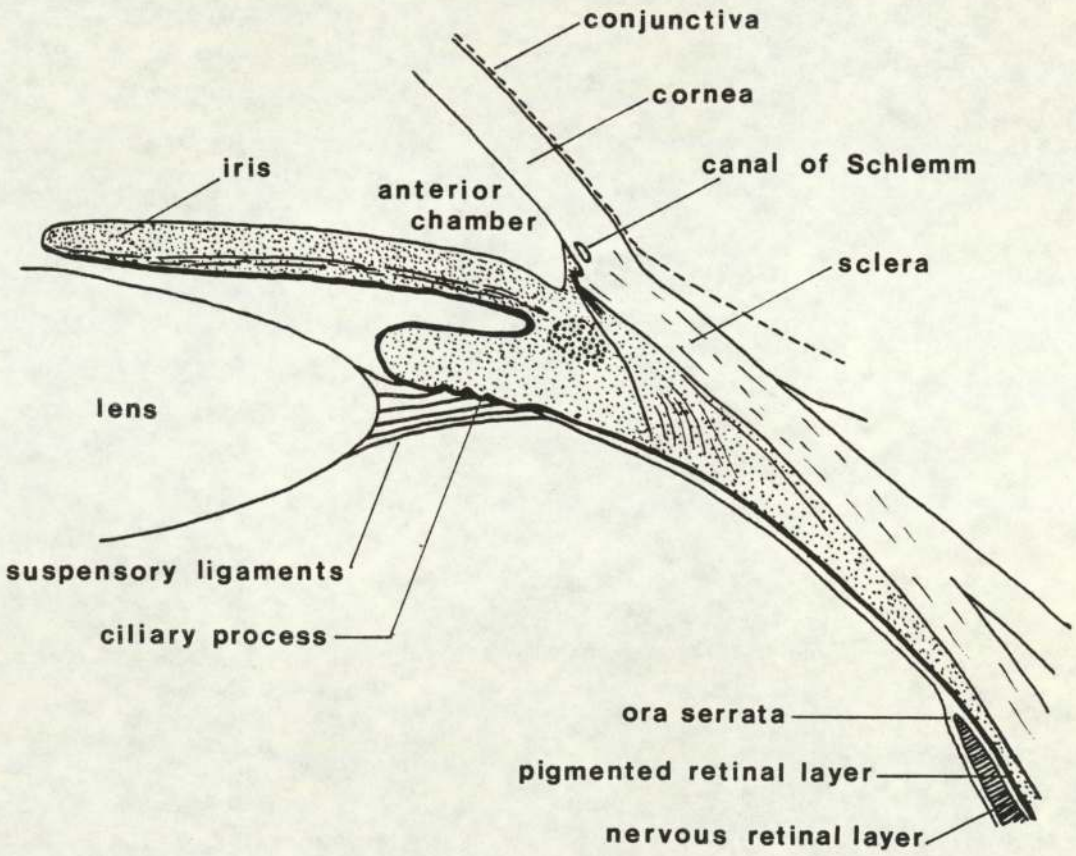
Both the epithelium and endothelium resist the diffusion of certain substances and act as semi-permeable membranes. Damage to either can result in stromal oedema due to water retention in the stromal layer.

3. The Iris

This thin circular disc, attached to the anterior surface of

the ciliary body, is perforated at the centre by the opening known as the pupil. It consists of two sets of muscles; the sphincter pupillae muscles, innervated by the parasympathetic nervous system and the dilator pupillae muscle, innervated by the sympathetic nervous system. The iris is highly vascular and contains pigment cells which give the colour to the eyes.

Figure 1.1.2 - The Ciliary Body



4. The Ciliary Body

This region is triangular in cross section. The iris originates from the middle of the anterior surface and the suspensory ligaments of the lens originate from the ciliary processes. The ciliary muscle; lying in the anterior and outer part of the ciliary body cause changes in the shape of

the lens, controlled by parasympathetic innervation. Aqueous humour production and secretion also occurs within the ciliary body.

5. The Choroid

This layer contains the vascular supply to the eye. The large vessels, mainly veins, are on the outermost surface, while the inner layer consists of chorio-capillaries. Pigment cells are scattered throughout the supporting connective tissue. Bruch's membrane separates the choroid from the pigment epithelium of the retina.

6. The Retina

The retina is a thin layer (approximately 0.4mm) which lines the posterior two-thirds of the globe. It has two parts, the inner transparent neural portion and the outer pigment epithelium. The neural retina is attached to the pigment epithelium only at the optic disc and its anterior margin. The junction between the retina and ciliary body is referred to as the ora serrata.

a) Pigment Epithelium - a single layer of flat cells attached to the inner layer of Bruch's membrane.

b) Neural Retina - this tissue contains the rods and cones responsible for distinguishing between light and dark and the visualisation of colour. It contains five types of neurones and specialised glial cells.

c) Optic Disc - the area where the optic nerve leaves the eyeball. No retina tissue is present and it is hence an area where no visual messages can be relayed. This is often

referred to as the "blind spot".

d) Fovea Centralis - a specialised area of the retina, responsible for sharp central vision. it is rich in rods and cones and lies on the central axis of the eyeball.

7. The Lens

This transparent biconvex body is 9 - 10mm in diameter and 4 - 5mm thick. It is crystalline in nature and is surrounded by a transparent, elastic membrane known as the capsule. The anterior epithelium is a single layer of cells on the anterior surface of the lens. It is attached to the ciliary body by suspensory ligaments and separates the aqueous and vitreous humours.

8. The Aqueous Humour

Similar in composition to protein free plasma, the aqueous humour fills the anterior and posterior chambers. It is secreted by the ciliary processes into the posterior chamber and flows through the pupil into the anterior chamber. It is then lost via the trabecular meshwork and the Canal of Schlemm into the blood vessels at the angle of the anterior chamber. It is the nutritive medium for the lens and cornea.

9. The Vitreous Humour

The vitreous is adjacent to the lens, pars plana of the ciliary body, the retina and the optic disc. Its shape is determined by the tissue surrounding it, but also by its own framework, elasticity and turgescence. It is firmly attached to the neighbouring tissues at the peripheral retina, ciliary body and optic disc. Collagen and hyaluronic acid

are responsible for the molecular structure.

10. The Conjunctiva

This thin mucous membrane lines the eyelids and is continuous with the epithelial layer of the cornea. The area attached to the eyelids is known as the palpebral conjunctiva, that covering the eyeball as the bulbar conjunctiva. Goblet cells in the conjunctiva secrete mucus which aids lubrication.

11. The Pre-corneal Film

To act as an optically adequate surface the cornea must be wet; when dry its transparency is lost. The pre-corneal or tear film, part of the tear fluids, provides this moist surface, and its character depends on the condition of the corneal epithelium. The film is composed of three layers, a thin outer lipid layer, thicker middle aqueous layer, and a thin inner mucoid layer. It is renewed by each blink and if blinking is suppressed will dry in patches. It seems to be unaffected by the addition of solutions of a concentration up to the equivalent of 2% w/v sodium chloride to the conjunctival fluid, but is deranged below pH 4 and above pH 9. [3]

1.1.2 Permeability of the Intraocular Blood Vessels

The anatomy of the capillary wall differs from one ocular tissue to another, as does the permeability of the blood vessels. Lipid-soluble or readily diffusable substances such as oxygen and carbon dioxide penetrate well into all tissues, while the passage of water soluble substances is restricted as they must pass through water-filled pores in

the capillary walls. There may also be some transendothelial transport of water-soluble substances by pinocytosis.

Retinal capillaries demonstrate a thick endothelium lacking fenestrations, the endothelial cells being held together by tight junctional complexes. Outside the endothelium is a thick basement membrane, containing intramural pericytes and in direct contact with glial tissue. The permeability of these blood vessels is similar to that of the vessels of the central nervous system, which gives rise to comparisons between the "blood-retinal" and "blood-brain" barriers. Although the capillary wall of the retinal vessels seems to be a tight barrier, this alone would not prevent the passage of substances into the retina if there were no barrier between the uvea and retina. The pigment epithelium of the retina is part of this additional barrier. The epithelial cells show tight junctions which appear to prevent the diffusion of many substances. [4,5,6]

The capillaries of the ciliary processes and choroid have thin walls with large fenestrations covered by a thin membrane. The junctions between endothelial cells are wide and short and a very thin basement membrane surrounds the capillary. The blood vessels of this tissue have a high permeability even to large molecules. Diffusion from the ciliary processes via the posterior chamber is thought to be a route by which larger molecules could enter the retina. However under normal conditions such movement is prevented by tight junctions of the pigmented cells of the ciliary processes. [7]

1.1.3. Drug Penetration into the Eye

The pharmacological behaviour of drugs in the eye is difficult to demonstrate. There are a wide variety of compartments within the eye; cornea, sclera, iris, retina, aqueous humour, vitreous humour etc. Some of these compartments show active transport of certain substances, for example the ciliary body possesses an active transport pump which removes organic anions such as penicillins. The eye may be treated by a number of routes including systemic (oral, intravenous, intramuscular), periocular (sub-conjunctival, sub - Tenon's, retrobulbar), topical (eye drops, eye ointments, inserts) and intraocular (intravitreal, intracameral). Each will have a different set of kinetics. In addition, the nature of the blood - ocular barriers is not fully understood, but they are thought to be similar in nature to the "blood - brain" barrier. Capillary permeability is thought to play an important role in the inaccessibility of the eye to drug penetration. [7,8,9]

1.1.4 Drug Transport Across the Cornea

The transport of drugs is determined by the permeability of the corneal layers. Many factors affect the drug penetration through the cornea, these may either be related to the drug solution or to the corneal layers. [10,11,12]

The epithelial and endothelial cell membranes are barriers rich in lipid, and are therefore more readily crossed by lipid-soluble compounds. The stroma is more easily crossed by water-soluble or hydrophilic substances. This combination

of layers is often referred to as presenting a "fat-water-fat" sandwich. To penetrate across the cornea, drugs must pass through barriers with different structural specificities and substances that are soluble in both will penetrate more freely. This has been demonstrated by Swan and White who studied the relative penetration of procaine and tetracaine. [13] These two compounds have the same basic structure, but differ in their polar and non-polar end-groups. The enhanced penetration of tetracaine over procaine is accounted for by the presence of a more polar group at one end and a less polar group at the other end with comparison to procaine. This experimental finding is reflected in the clinical fact that tetracaine is an effective corneal anaesthetic at a concentration of 0.5%, while procaine is ineffective at 2%.

The pH and osmolarity of solutions are also important in the penetration of solute through the cornea. Most commonly used ophthalmic solutions are buffered by weak acid - salt combinations, for example citric, boric or phosphoric acid - salt combinations. Although in the past it was common practice to adjust the tonicity of eye drops to make them isotonic with tears, it is now thought that the eye can tolerate solutions having a range of equivalents from 0.6 - 2% w/v sodium chloride. A very hypotonic solution may cause temporary corneal oedema and grossly hypertonic solutions tend to produce discomfort due to the inability of the tears to adequately dilute the solution. The epithelial permeability is considerably increased by hypotonic solutions. Potts [14] found the tonicity that least damages

which he infers to be the tonicity of tears.

Tears have a considerable capacity to buffer solutions which are instilled into the conjunctival sac to their normal pH of 7.4. The epithelial permeability is unchanged within the pH range 4 - 10, but increases outside this range. [3]

Those agents that reduce surface tension increase the permeability of membranes. O'Brien and Swan showed that the transcorneal penetration of the non lipid soluble drug carbachol is greatly enhanced by the presence of benzalkonium chloride, a surface active agent commonly used in eye drop formulation as a preservative. [15]

The viscosity of the solution has been shown to influence the degree of penetration from ophthalmic products. This is due to the prolonged contact time with the eye of a viscous product. Substances such as methylcellulose, polyvinyl alcohol and hydroxymethylcellulose (hypromellose) are frequently added to increase viscosity. Hardberger, Hanna & Boyd found that the penetration of radioactive ^{99m}Tc applied to the cornea of human eyes was enhanced in vehicles containing methylcellulose and polyvinyl alcohol, when compared with the penetration from a saline solution. [16]

It has been found that generally the increase of viscosity up to the 25 - 50 centipoise range increases contact time in the eye. Higher viscosity values tend to offer no significant advantage. [3]

1.1.5 Routes of Administration to the Eye

The generally poor response of serious ocular infections to

systemic or topical treatment is due to poor penetration of the antibiotic into the affected tissues.

1. Topical Administration

Although topical administration results in high concentrations of drug in the anterior structures, such as the conjunctiva and cornea, much lower concentrations are achieved in the anterior chamber, and minimal concentrations in the posterior ocular structures, the vitreous, retina and choroid. [17]

Penetration of drugs into the eye following topical administration depends on their lipophilicity. [8] For a drug to penetrate the eye following topical administration, it must pass through a "fat-water-fat" sandwich so must have the ability to exist in solution at an equilibrium between ionised and non-ionised forms.

2. Systemic Administration

Following systemic administration a drug has to cross the "blood-retinal" barrier, similar in nature to the "blood-brain" barrier. Therefore relatively small concentrations of hydrophilic drugs such as penicillins, cephalosporins and aminoglycosides will be found in the aqueous and vitreous humours even if high doses are administered. In contrast lipophilic drugs such as chloramphenicol and some tetracyclines will readily cross the "blood-retinal" barrier. [8]

3. Periocular Injections

Higher concentrations of drug can be obtained in ocular

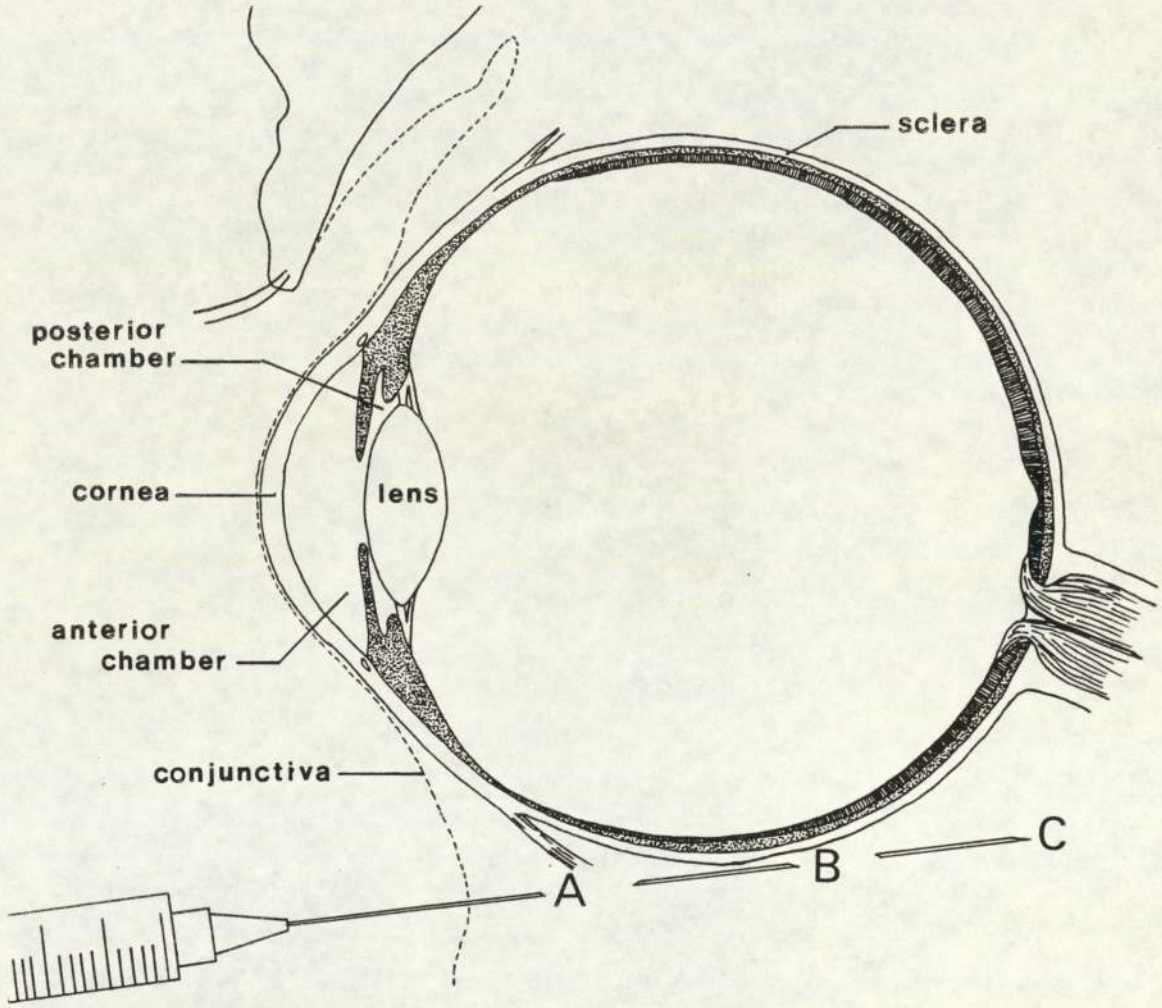
tissues by periocular injection than by a much larger dose given systemically. [8,18-23] The highest concentration of drug is present in the aqueous and anterior structures, such as the cornea and conjunctiva making it most suitable for the treatment of corneal infections. [24] It is still difficult to obtain high concentrations in the vitreous humour following subconjunctival injection; [25,26,27] intraocular injection is necessary for drug delivery to this area. [28-31]

Periocular injections are given into the tissues surrounding the eye and there are three main types of periocular injection; subconjunctival, sub-Tenon's and retrobulbar.

a) Subconjunctival Injection

A subconjunctival injection is probably the most commonly used periocular injection, especially for the administration of antibiotics. Injection is made into the subconjunctival space between Tenon's capsule and the conjunctiva, forming a bleb of fluid. The fluid spreads by dissecting under the conjunctiva and it is thought to penetrate the eye by two routes. Leakage from the bleb through the needle track into the tear film allows transcorneal absorption, while direct penetration into the sclera and cornea, trabecular meshwork and ciliary body allows penetration into the anterior chamber. Highest concentrations are found close to the site of injection. The eye is anaesthetised with a topical local anaesthetic before the injection is made. [32]

Figure 1.1.3 - Relative Positions of Periocular Injections



A - Subconjunctival, B - Anterior Sub - Tenon's,
C - Posterior Sub - Tenon's

b) Sub - Tenon's Injection

There is little difference between an anterior sub-Tenon's injection and a subconjunctival injection and the terms are frequently interchanged. The site is slightly different and a lower quantity of drug appears to be delivered to the eye. Injection is carried out in a similar way to subconjunctival injection but using a longer needle. It is important to ensure that the globe is not accidentally

perforated, as the site of delivery is much closer to the globe, and blood aspiration should be attempted prior to injection to ensure that injection is not made directly into a blood vessel. [32]

Posterior sub-Tenon's injection is commonly used to deliver corticosteroids to the more posterior ocular structures, in the treatment of posterior and intermediate uveitis, and macular inflammation. The site of injection is similar to that achieved with a retrobulbar injection but is usually considered to be more comfortable for the patient.

c) Retrobulbar Injection

Retrobulbar injection was originally developed to induce anaesthesia of the globe, and this is still its principal use. However antibiotics, steroids and alcohol are also given by this route. Retrobulbar steroids are frequently used in the treatment of posterior inflammatory diseases. A retrobulbar injection will achieve similar levels to those seen with a subconjunctival injection in the posterior ocular structures, but lower levels in the anterior structures, a reason why it is usually reserved for the treatment of posterior disease. The injection is made into the area around the ciliary ganglion, within the muscle cone surrounding the orbit. [32]

Considerations in Periocular Injection Preparation

There are many considerations necessary in preparing an injection for periocular administration. Some are common to any product intended for injection. The solution should be

sterile, isotonic and not at extremes of pH. Others are specific to this group of injections. Unless unavoidable the solution should be free from excipients such as preservatives. This is not always possible as some drugs are only commercially available in one formulation. However where a choice exists, a non-preserved product should be used. Lignocaine and adrenaline may be used as a diluent to decrease pain at the injection site and decrease systemic absorption. [32,33]

The volume given by subconjunctival and sub-Tenon's injection should not exceed 0.5ml at one site, as this increases the likelihood of pain and tissue damage, and a dose requiring a larger volume should be divided between two sites. However, in practice, larger volumes are given by some ophthalmologists. The volume given by retrobulbar injection varies depending on the type of drug being given. For anaesthetic solutions the volume may vary between 1.5 and 6.0ml, while for other drugs a smaller volume is usual.

There is some disagreement whether these injections should be prepared only as solutions, or whether suspensions are acceptable. A suspension may require the use of a larger bore needle to allow administration, but may result in a longer acting injection.

Complications of Periocular Injections

While periocular injections are an effective method of delivering drugs to the eye, their use is not without risk. It is debatable whether they should be used as routine treatment or reserved for emergency situations or for those

It is debatable whether they should be used as routine treatment or reserved for emergency situations or for those cases where more conventional treatment has failed. Accidental perforation of the globe is probably the most serious consequence of periocular injection, and is more likely with retrobulbar and sub-Tenon's injection, which pass closer to the globe itself. Less serious complications include pain, eyelid swelling, ptosis (eyelid drooping), conjunctival oedema and haemorrhage. Patient apprehension about a procedure of this nature is also likely to be high.

4. Intraocular Injections

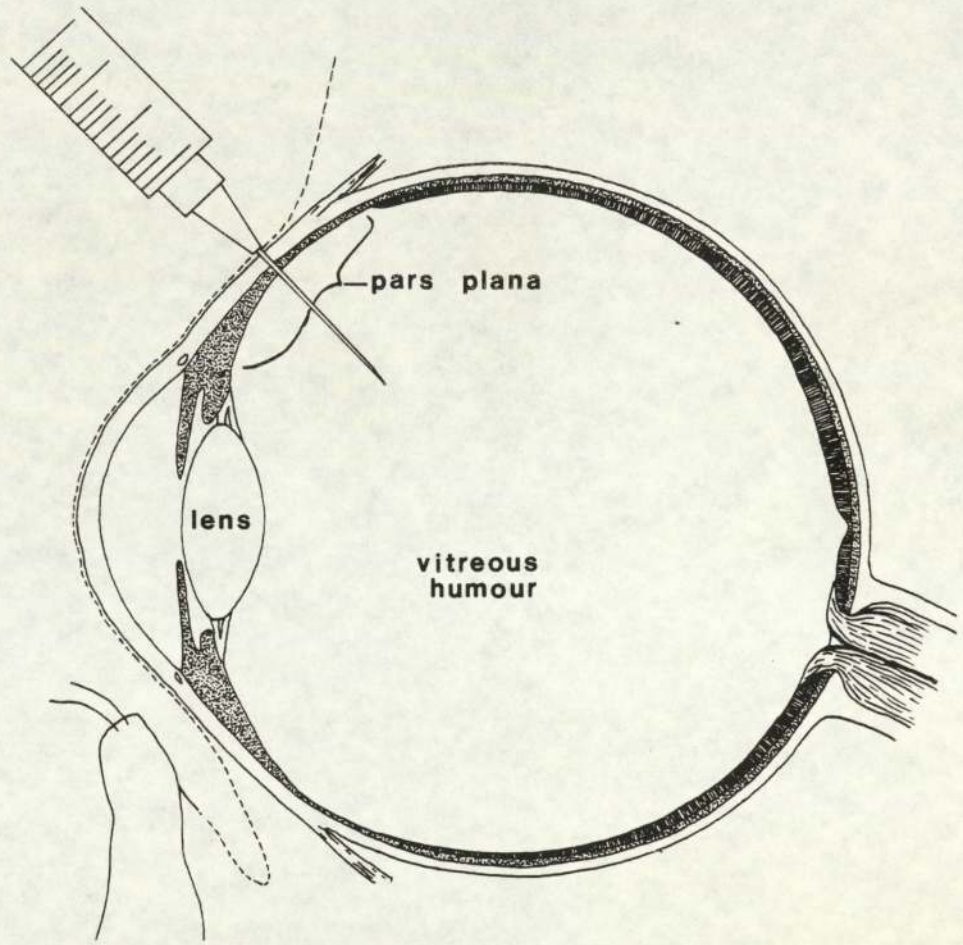
Intraocular injections are, as the name suggests, injection into the eye itself. There are two areas into which an injection can be made. Intravitreal injection into the vitreous body, and intracameral injection into the aqueous humour or anterior chamber. The administration of a solution of incorrect strength can have disastrous consequences and may result in loss of vision.[34]

a) Intravitreal Injection

It remains difficult to obtain high levels in the vitreous following periocular injection,[25,26,27] and the intravitreal penetration of antibiotics is also relatively low following systemic and topical administration.[8,35,36,37] As the prognosis of intraocular infection (endophthalmitis) is poor when treated by topical, systemic or periocular administration, direct injection into the vitreous is used.[29,30,31] Intravitreal injection may be carried out with or without vitrectomy being performed.

out injection is made into the pars plana area. As the cause of endophthalmitis is rarely known, combinations of

Figure 1.1.4 - Position of Intravitreal Injection



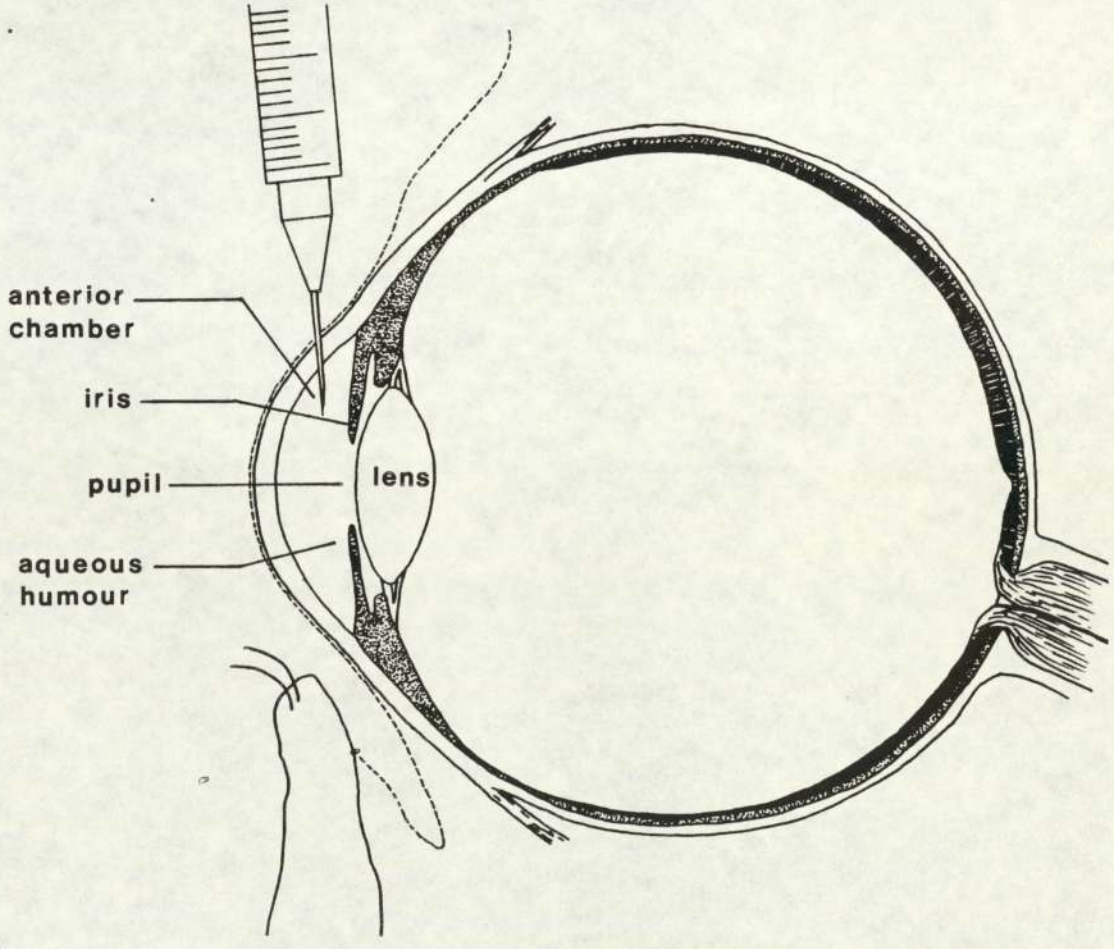
antibiotics may be used, often with the addition of a corticosteroid to decrease inflammation.[38] Following injection the drug diffuses throughout the vitreous and is eventually lost by diffusion into the aqueous humour or lost directly across the retina. The procedure is usually carried out in the operating theatre under general anaesthetic, or with retrobulbar and topical anaesthesia.

b) Intravitreal Infusion

Recently therapeutic vitrectomy has been introduced as a

therapy for endophthalmitis. The vitreous is removed, along with the infecting agent and inflammatory cells. During the vitrectomy an antimicrobial containing solution is used to irrigate the area and may be left in the eye as a replacement for the vitreous. [39-42] This is referred to as an intravitreal infusion. Although this procedure appears to be used in the United States, it does not yet seem to be accepted in the UK. It is generally felt to be less safe than intravitreal injection, as it is impossible to know exactly what dosage has been administered. [43,44,45]

Figure 1.1.5 - Position of Intracameral Injection



c) Intracameral Injection

Intracameral injection involves the injection of a drug

directly into the anterior chamber. As high concentrations can usually be obtained in the aqueous humour following subconjunctival and topical treatment, the use of intracameral injection is relatively rare. It may however be considered in the treatment of non-sterile conditions requiring surgery, such as the closure of a penetrating wound or repair of a ruptured operative wound. Intracameral injection is also a theatre procedure carried out under general anaesthetic or with retrobulbar and topical anaesthesia. [32,46]

Considerations in Intraocular Injection Preparation

As with any injection a solution used by these routes should be sterile and isotonic. It should also be free from excipients, such as preservatives, as some of the preservatives have been reported to cause retinal toxicity. The pH of the solution is not as important for intravitreal injection as it is for periocular injections, as the volume administered is highly diluted on injection, resulting in a change to the pH. However it is still prudent to avoid solutions at extremes of pH wherever possible.

The volume of solution injected by intracameral and intravitreal injection, when no vitrectomy has been carried out should not exceed 0.1ml. The volume of an intravitreal infusion is determined by the volume of the vitreous. Of more importance is the concentration of drug in the solution being used.

Complications of Intraocular Injections

Only very minute amounts of drug can be tolerated by the

anterior and posterior chambers. Excessive concentrations can result in serious damage to ocular tissues, and retinal toxicity is the most important complication of intravitreal injection. Intracameral injection may be complicated by the development of corneal opacities, loss of corneal endothelium and vasculisation of the cornea.

1.2 METHODS

The objective of this part of the project was to investigate the practices of hospitals treating ophthalmic patients with regard to ophthalmic injections and extemporaneously prepared eye drops.

The Pharmaceutical Department at the Birmingham and Midland Eye Hospital frequently receives requests for information about the dosage and preparation of periocular and intraocular injections and the preparation of extemporaneously dispensed eye drops. The major national source of reference currently available for both these subjects is the Moorfields Eye Hospital Pharmacopoeia. This contains recommended formulae for many eye drop preparations and dosage recommendations for ophthalmic injections. Apart from this information source reference must be made to original papers on the subject.

Periocular and intraocular injections are a method of administration, mainly used for antibiotics and corticosteroid preparations, which is frequently needed in the treatment of patients with diseases of the eye. Higher concentrations of drug can be obtained in ocular tissues by these routes than by either a much larger dose given systemically, [8,35] or by intensive topical therapy.[36,37] Such injections are commonly administered in theatre and are diluted from vials intended for systemic use to provide the appropriate concentration. On some occasions more than one dilution step is necessary, and concern has been expressed by members of the surgical staff at the risk of error due to

the absence of written guidelines. The administration of a solution of incorrect strength can have disastrous consequences and may result in loss of vision. [34]

A number of drugs required for the topical treatment of ophthalmic conditions are not available commercially. Therefore, when these are requested, they must be prepared extemporaneously. Often this consists of a simple solution of the drug in Water for Injections BP, sterilised by terminal filtration. In many cases the shelf life assigned to these products is based on work carried out on parenteral preparations, where the strength may be of a different magnitude. Such preparations are often given an arbitrary limited shelf life of 24 hours due to the risk of contamination. They are therefore costly and time-consuming to prepare.

1.2.1 Selection of Questionnaire Recipients

Having identified the production of ophthalmic injections and extemporaneously prepared eye drops as areas where the availability of further information would be valuable it was decided to find out whether the same problems were encountered by other hospitals treating ophthalmic patients. To achieve this a questionnaire was designed requesting information about the usage of anti-infectives and corticosteroids by ophthalmic injection and extemporaneously prepared eye drops.

The questionnaires, together with a covering letter and a reply envelope, were distributed by post to hospital pharmaceutical departments. The pharmaceutical departments

were selected from the mailing list of a major manufacturer of ophthalmic preparations and validated against the Hospital Year Book [47] as those hospitals having dedicated ophthalmic beds.

1.2.2 Questionnaire Design

1.2.2.1 Pilot Study

A questionnaire consisting of six questions relating to the use of ophthalmic injections was designed for use in a pilot study to assess the suitability of the questionnaire. Questions included: i) the form in which these injections were issued; whether as the original vial - with or without information, or as a ready prepared injection, ii) the annual usage of drugs by these routes, to be completed in a precompiled table, iii) the product usually used, for administration by these routes, iv) any information regarding stability, shelf life and storage conditions of the finished product held at the centre, v) any information about mixing these injections and the subsequent stability of the mixed injection, and vi) whether the respondent was interested in receiving further information about preparation and administration of ophthalmic injections (See Appendix I).

Considering the small doses that are used for these types of injection, and the degree of wastage involved when an injection is prepared from a vial intended for parenteral use, a question was included to assess the degree of interest in a national service for providing these injections.

This initial questionnaire was distributed to 16 hospital pharmaceutical departments.

1.2.2.2 Revised Questionnaire

Following responses to the pilot mailing the design of the ophthalmic injection questionnaire was revised, and a companion questionnaire relating to the use of extemporaneously prepared eye drops was designed. The questionnaire relating to extemporaneously prepared eye drops consisted of two questions: i) the annual usage of these products, to be completed in a precompiled table, including pharmaceutical details, such as the strength, vehicle or formula used, preservative, shelf life and storage conditions, and ii) the source of any information about the stability of these products on which the shelf life and storage conditions are based. (See Appendix II)

From the responses received to the initial mailing the layout of the questionnaire was modified to allow easier completion, details of the recipient were included on the questionnaire, to decrease the amount of information necessary to be completed, and a question relating to demographic data was included in order to classify and validate the sample.

The two questionnaires were distributed by post, together with a covering letter and reply envelope, to the pharmaceutical departments of 110 hospitals, including those approached in the pilot study. After three months a second set of questionnaires, covering letter and reply envelope were distributed to those hospital pharmaceutical

departments which had not responded to the first request. Any responses to returned questionnaires which were unclear or ambiguous were followed up by telephone with the person or people who had filled in the questionnaire.

1.3 RESULTS

1.3.1 Respondent Characteristics

Responses were received initially from 49 (44.5%) centres which increased to 78 centres (70.9%) following the second mailing and follow up by telephone. Replies to the extemporaneous eye drops questionnaire were not always accompanied by the ophthalmic injection questionnaire, which were received from 74 hospitals (67.3%).

Of these nine centres no longer had dedicated ophthalmic beds or had closed and become part of larger hospitals. These have not been included in any statistical analysis of the data. Of the total 152 questionnaires returned seven (4.6%) were completed by technical staff, one (0.6%) by a member of the medical staff, 79 (52.0%) by female pharmacists and 65 (42.8%) by male pharmacists. In a number of cases the eye drop and ophthalmic injection questionnaires were completed by different people. The proportion of female : male pharmacists who responded is similar to the proportion working in hospital pharmacy as a whole. [48]

Table 1.3.1 Respondant Characteristics

	Female	Male
Technical Staff	6	1
Pre-registration Pharmacists	2	-
Basic Grade Pharmacists	14	3
Staff Pharmacists	46	34
Principal Pharmacists	14	23
DPhO	1	5
Medical Staff	-	1

(total number of questionnaires completed = 152)

1.3.2 Ophthalmic Injections

1.3.2.1 Usage of Intraocular and Periocular Injections

1.3.2.1.1. Periocular Injections

A total of 74 replies to the ophthalmic injections questionnaire were received. Antimicrobial and corticosteroid agents were reported to be administered by subconjunctival injection at most centres. The aminoglycosides were reported as the most commonly used group of antimicrobial drugs, with gentamicin used at 47 centres (63.9%) and framycetin at 17 (23.61%). Ofthe penicillins methicillin was stated to be used at 38 centres (52.8%), and benzylpenicillin was used at 12 centres (16.7%). Cefuroxime was reported as the most commonly used cephalosporin, which was listed at 12 centres (16.7%). Other periocular injections of antimicrobial agents included, chloramphenicol, clindamycin, erythromycin and vancomycin.

Corticosteroids were reported to be administered by periocular injection at a large number of centres, with respondants often listing more than one type of steroid. Betamethasone was reported to be administered at 33 centres (45.8%) and methylprednisolone at 23 (31.9%). Other steroids listed included dexamethasone and triamcinolone.

Few hospitals appeared to administer antifungal agents by periocular injection, with amphotericin and miconazole the only agents which were reported to be used by this route.

1.3.2.1.2 Intraocular Injections

Antimicrobial and antifungal agents were reported to be administered by intraocular injection at far fewer

Table 1.3.2 - Usage of Intraocular and Periocular Injections

Drug	percentage of hospitals using		
	sub-conjunctival injection	intra-cameral injection	intra-vitreal injection
Ampicillin	5.6	-	-
Benzylpenicillin	16.7	-	4.2
Methicillin	52.8	1.4	12.5
Mezlocillin	1.4	-	1.4
Piperacillin	1.4	-	-
Ticarcillin	2.8	-	-
Cefotaxime	4.2	-	4.2
Ceftazidime	4.2	-	1.4
Cefuroxime	16.7	-	2.8
Cephalothin	1.4	-	-
Cephazolin	8.3	-	4.2
Cephradine	1.4	-	1.4
Amikacin	-	-	1.4
Framycetin	23.6	-	1.4
Gentamicin	63.9	2.8	16.7
Kanamycin	1.4	-	1.4
Tobramycin	5.6	-	1.4
Chloramphenicol	1.4	-	-
Clindamycin	1.4	-	1.4
Erythromycin	1.4	-	-
Lincomycin	1.4	-	-
Vancomycin	4.2	-	2.8
Amphotericin	2.8	1.4	4.2
Miconazole	1.4	1.4	2.8
Betamethasone	45.8	-	1.4
Dexamethasone	13.9	-	-
Methylprednisolone	31.9	-	-
Triamcinolone	9.7	-	-

(Number of respondants = 74)

centres than periocular injections. The aminoglycosides were the most commonly described group of antimicrobial drugs, with gentamicin reported from 12 centres (16.7%) Of the penicillins, the most frequently used was methicillin, which was listed at 9 centres (12.5%). Of the cephalosporins

cefuroxime, ceftazidime, cephradine and cefuroxime were reported to be used. Other antimicrobial agents given by intraocular injection included vancomycin and clindamycin.

Only one centre reported the use of corticosteroids by intraocular injection.

Use of intraocular injections of antifungal agents was reported from more centres than use of them by periocular injection.

1.3.2.2 Form in Which Injection Issued

It was apparent from the questionnaire that in 69.5% of hospitals injections vials alone were issued when injections of this type were requested. At the opposite end of the spectrum 8.3% of respondents provided a service for

Table 1.3.3 - Form in which Injections are Issued

Form	
Injection vial only	69.5%
Injection vial plus information regarding dilution	27.8%
More than one category issued depending on drug and injection type	16.2%
Single-dose ready prepared injection	8.3%

(number of respondants = 74)

preparing single-dose injections ready for administration to the patient. Of those hospitals who reported that they issued injection vials alone, 16.2% claimed to issue,

with the injection vials, dilution information in some cases, depending on the drug and type of injection involved. 27.8% of respondants always issued the injection vial with information regarding dilution.

1.3.2.3 Availability of Information

Although 27.8% of hospitals replied that at least some injections were issued with information regarding dilution to an appropriate dose, only 6.9% felt that they had sufficient information available to meet their needs, and 79.2% were interested in the availability of further information about these types of injections.

56.9% of respondents were interested in the provision of a National Service for the preparation of ophthalmic injections.

Table 1.3.4 - Availability of Information

	Yes	No
Information currently available at hospital	6.9%	50.0%
Interest in further information	79.2%	5.6%

(NB. only 60 of 74 respondants answered these questions)

1.3.3 Extemporaneously Prepared Eye Drops

1.3.3.1 Usage of Extemporaneously Prepared Eye Drops

A total of 78 replies were received. It was clear from the questionnaire that despite many hospitals using the recommendations of the Moorfields Eye Hospital Pharmacopoeia when preparing eye drops, other hospitals were using simple

solutions even when a formula containing buffers and preservatives was available.

The most common extemporaneously dispensed ophthalmic preparations were antimicrobials. Penicillins were the most common group, of which benzylpenicillin was reported to be the most frequently prepared, at 66.7% of hospitals. Although a number of strengths of benzylpenicillin eye drops were reported the most popular was 5,000 units/ml, used at 18 of the 52 (34.6%) centres using it. This was followed by methicillin eye drops reported by 37.2% of respondents.

Table 1.3.5 - Usage of Extemporaneously Prepared Eye Drops

Drug	%	Drug	%
Ampicillin	2.6	Amikacin	1.3
Benzylpenicillin	66.7	Gentamicin (1.5%)	24.4
Carbenicillin	6.4	Tobramycin	1.3
Methicillin	37.2		
Ticarcillin	11.5	Colistin	5.1
		Streptomycin	1.3
Cefotaxime	6.4	Vancomycin	7.7
Ceftazidime	11.5		
Cefuroxime	30.8	Amphotericin	12.8
Cephalothin	1.3	Clotrimazole	10.3
Cephazolin	11.5	Econazole	3.9
Cephradine	1.3	Miconazole	3.9
		Nystatin	5.2
Ciprofloxacin	1.3	Natamycin	3.9
		F3T	5.2

(number of respondants = 78)

The next most commonly prepared group of antimicrobials were the cephalosporins; cefuroxime being the most popular - reported from 30.8% of hospitals.

Of the aminoglycoside group, gentamicin was most frequently prepared as 1.5% eye drops. Amikacin and tobramycin were

also reported.

Of the antifungal preparations amphotericin was most widely reported. Trifluorothymidine (F3T) was the only antiviral eye drop reported to be extemporaneously prepared, and this only by four centres (5.1%).

Other antimicrobial eye drops reported in small quantities included ciprofloxacin, colistin, streptomycin and vancomycin. Extemporaneously dispensed eye drops, prepared other than for antimicrobial effects which were reported in the questionnaires, included potassium ascorbate to treat alkali burns, thiotepa for the treatment of pterygium, acetylcysteine used in the treatment of dry eyes, and a number of dilutions of products available commercially.

1.3.3.2 Sources of Stability Information

24 (30.8%) hospitals responded positively to having stability information on which they base the quoted shelf life.

Table 1.3.6 - Sources of Stability Information

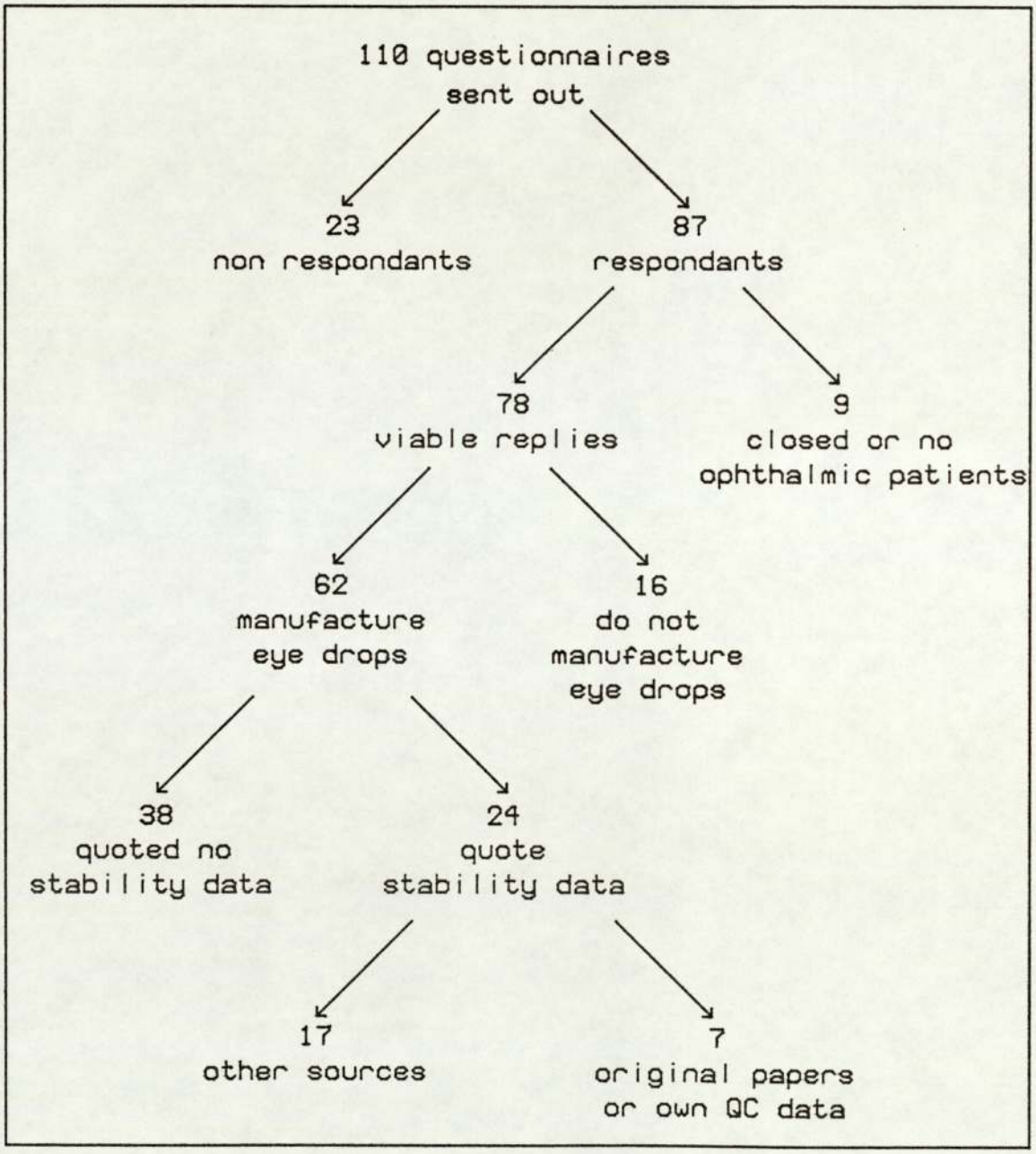
Source	percentage
Moorfields Pharmacopoeia	29.2
Trissel	12.5
Martindale / British Pharmacopoeia	12.5
Original Papers	20.8
Drug Company / Datasheet	29.2
Own QC data	8.3

(number of respondants = 24)

In 29.3% of cases these were based on original papers or work carried out in Quality Control Laboratories, while the

rest were obtained from other sources. This information is summarised in Figure 1.3.1.

Figure 1.3.1 - Proportion of Respondants Using Original Data for Stability of Extemporaneously Prepared Eye Drops



1.4 DISCUSSION

From the responses to the questionnaires it was seen that antimicrobials were the most commonly prepared eye drops and ophthalmic injections.

Of the penicillins benzylpenicillin was the most commonly prepared eye drop followed by methicillin. However, methicillin was the most frequently prepared ocular injection. There is a difference in the antimicrobial spectrum of these two drugs. At the ophthalmic hospital in the West Midlands region (The Birmingham and Midland Eye Hospital) benzylpenicillin is the antibiotic of choice for infections caused by streptococci, Neisseria and Actinomyces species while methicillin is used for penicillinase-producing Gram-positive organisms. However benzylpenicillin is very painful to administer and many centres administer it mixed with lignocaine and adrenaline.[35,48] The administration of a subconjunctival injection of methicillin is sometimes preferred, especially when treating an infection from which no results from bacterial cultures are available.

The next most commonly prepared group of antimicrobials was the cephalosporins: cefuroxime was both the most frequently prepared ocular injection and eye drops. However, no reports of the stability of cefuroxime in eye preparations or its penetration into the eye from these formulations are available. This may reflect the dearth of literature from the UK in this area. Most of the documented evidence stems from studies in the USA where cefuroxime is not marketed. In

the USA most studies with cephalosporins have involved cephazolin, [49-55] particularly by intravitreal injection, [49,51,56-59] but in this survey only seven centres used cephazolin and one of those also used cefuroxime.

Of the aminoglycosides group, gentamicin was most frequently prepared as 1.5% eye drops and as a subconjunctival and intravitreal injection. A 0.3% eye drop formulation is available commercially, but penetration of the drug is reported to be poor, yielding subtherapeutic amounts in the aqueous humour. [60,61,62] It is perhaps of concern that gentamicin is the most frequently prepared intravitreal injection, as there is evidence to suggest that it is the aminoglycoside that shows the greatest toxicity to the retina. [63]

It is interesting that framycetin is widely prepared as a subconjunctival injection as the eye drops are commercially available. One report states that the eye drops are clinically effective in superficial infections but does not present any data on penetration. [64]

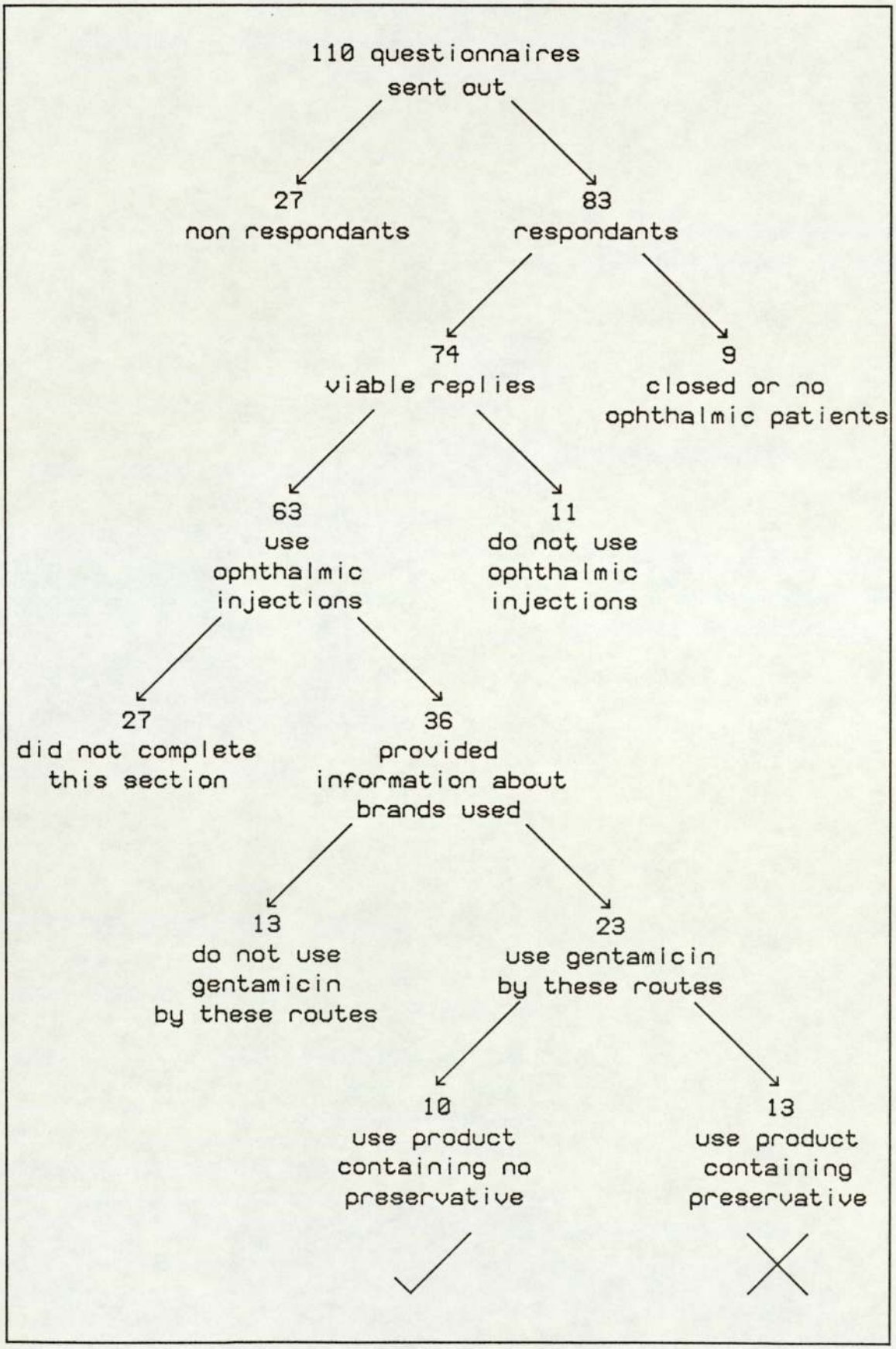
Reviewing the eye drops with a similar spectrum of activity is also interesting. Of those with activity against Pseudomonas species carbenicillin is the most widely used, followed by ceftazidime, with one centre reporting the use of ciprofloxacin. Carbenicillin is reported to penetrate the inflamed eye in sufficient concentration following a 5g intravenous dose, [8,24,50,64] but not to penetrate the eye following topical application. [36]

Following intravenous administration of ceftazidime it achieves concentration in the aqueous that are inhibitory to sensitive organisms including Pseudomonas aeruginosa. [66,67] Ciprofloxacin attains inhibitory concentrations in the aqueous after intravenous or multiple oral doses, but no evidence appears to exist of penetration following the topical administration of eye drops. [68-71]

Of the antifungal preparations amphotericin is most widely prepared, especially formulated as eye drops. Both amphotericin and miconazole are prepared as ophthalmic injection much less frequently. They both usually cause pain at the site of injection. The preparation of only one antiviral agent as an eye drop, trifluorothymidine (F3T), is probably accounted for by the commercial availability of acyclovir, idoxuridine and vidarabine. Although no hospitals included in our survey reported the use of antiviral agents by ophthalmic injection, both acyclovir and ganciclovir have been reported in the literature as being used in the treatment of AIDS-associated retinitis by these routes. [72-78]

As a result of the ophthalmic injection questionnaire it became clear that although these types of injection are commonly used, often little is known about the criteria for preparing them. Of the 36 hospitals (48.7%) who completed the question asking which products they used to prepare these injection many reported that they were using products which are in fact unsuitable for use by these routes.

Figure 1.4.1. - Formulations of Gentamicin Used by Ophthalmic Injection



For example 23 hospitals report the use of gentamicin by these routes and quote the product used to prepared them. Of these 13 (56.5%) hospitals, including one specialist eye hospital, reported the use of formulations of gentamicin for the preparation of subconjunctival injection which contain excipients, when a preferable product is available which is excipient free. Only 10 (43.5%) hospitals reported the use of a product considered to be suitable. Not surprisingly of these ten hospitals 50% were either specialist eye hospitals or hospitals known to have a particularly strong involvement with ophthalmology. This information is summarised in Figure 1.4.1.

It became clear that a publication that collated guidelines for the preparation of these types of injection, suitable dosage recommendations and some background to what these injections actually were would be the most appropriate way to overcome this problem. At least one questionnaire was returned with the comment that "they were nor sure if they had answered it correctly as they weren't quite sure what these injections were". In many hospitals where ophthalmology has only a small place among a large number of other disciplines, this may not be surprising.

An extensive literature search was carried out and comprehensive information obtained. The criteria for both types of injection had to be considered. A subconjunctival injection should not have a volume of more than 0.5ml and should not be at extremes of pH or tonicity as local tissue

damage can occur. [32,33] Unless unavoidable, no excipients should be present but lignocaine and adrenaline may be used as a diluent to decrease pain at the injection site and drug loss to the systemic circulation, thereby increasing penetration. An intravitreal injection should not exceed 0.1ml due to the finite volume of the globe. The pH is not as critical as for a subconjunctival injection as the volume given is small in comparison to the volume of the vitreous and it is considerably diluted on administration.

Information was also compiled about the clinical and experimental use of antibiotics, antifungals, antivirals and corticosteroids by these routes. From this it was possible to decide appropriate doses which appeared to be both safe and effective and were supported by experimental data. Where several doses appeared in the literature it was decided to quote a dose range. In some cases the only data available are toxicity studies carried out on animals, normally rabbits.

It was also necessary to decide which of the available formulations for each antibiotic was most suitable for use, considering the criteria previously mentioned. From this information a series of tables were compiled (Appendix III) concerning dosage, diluent, reconstitution and dilution procedures. These were submitted to the manufacturer of each preparation for comment and also to the Division of Ophthalmology within the District. Revisions were then made as appropriate.

1.5 CONCLUSIONS

There was a close parallel between the preparation of extemporaneous antimicrobial eye drops and the use of subconjunctival and intravitreal injections of the same antibiotic.

The responses received to the questionnaires indicated that the provision of information on the subject of ophthalmic injection was desirable and necessary. Indeed the current practice in some hospitals may be considered dangerous in some instances.

Following an extensive literature search it is clear that information concerning the dosage and administration of ophthalmic injections is available in numerous original papers but no one publication exists which draws together this information. This information is presented in Appendix III as a booklet which:

i) provides dosage recommendations for ophthalmic injections

ii) provides information about appropriate diluents and products to use

iii) provides clear directions for reconstitution and dilution to provide a final solution of a concentration suitable for administration by these routes.

The most commonly prepared eye drops were benzylpenicillin, methicillin and cefuroxime. Although there have been several studies on the formulation and stability of penicillin eye drops we have been unable to find any documented evidence in

the literature to support the formulation of cefuroxime eye drops. However with the emergence of methicillin resistant micro-organisms there is a need for an effective ophthalmic preparation to treat infections caused by them. As cefuroxime eye drops seemed to be the most widely reported preparation it was decided to investigate the stability of an eye drop formulation of this drug.

PART 2

THE STABILITY OF CEFUROXIME SODIUM IN ARTIFICIAL TEAR SOLUTIONS AND AQUEOUS VEHICLES

2.1 INTRODUCTION

The objective of this section of the study was to explore the stability of cefuroxime eye drops formulated in a number of artificial tear solutions.

Cefuroxime is a second generation cephalosporin with antibacterial activity against most of the common organisms involved in ocular infections, including methicillin-resistant Staph. aureus. [80]

Cefuroxime has been available as the sodium salt for parenteral administration since 1975. The recent development of an esterified prodrug cefuroxime axetil has made oral administration possible. Cefuroxime shows a greater degree of stability to the beta-lactamases produced by Gram negative organisms than some other cephalosporins. [81] Organisms sensitive to its bactericidal action include Staph aureus, Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae, Escherichia coli, Klebsiella pneumoniae and Proteus mirabilis. Cefuroxime however is not effective against Pseudomonas aeruginosa. [80]

Several studies have shown that the parenteral administration of cefuroxime produces concentrations in the aqueous humour sufficient to exceed the minimum inhibitory concentration (MIC) of a number of common organisms. [82,83,84] As there is often difficulty in isolating causative organisms in ocular infections a broad spectrum antibiotic is necessary for initial treatment. Investigation of the blood concentration obtained following oral administration of cefuroxime axetil has demonstrated blood concentrations

comparable with those obtained from parenteral administration. [85,86] Although no work appears to have been reported on cefuroxime concentrations obtained in the eye after oral administration in humans, several groups have reported clinical success in the treatment of ocular infections by this route. [87,88,89]

The findings of the questionnaire discussed in Part 1 of this thesis showed that an ophthalmic preparation of cefuroxime sodium is often administered topically in the treatment of ocular and periocular infections. Because it is not available commercially it must be prepared extemporaneously, which is usually achieved by reconstitution of cefuroxime sodium powder for injection in sterile water. This product does not contain a preservative, and might be expected to deteriorate or become contaminated during storage.

The preparation of cefuroxime sodium in an artificial tear solution would be preferable because of the ability of a viscous vehicle to prolong pre-corneal drug retention and hence drug penetration. [18,90,91,92]

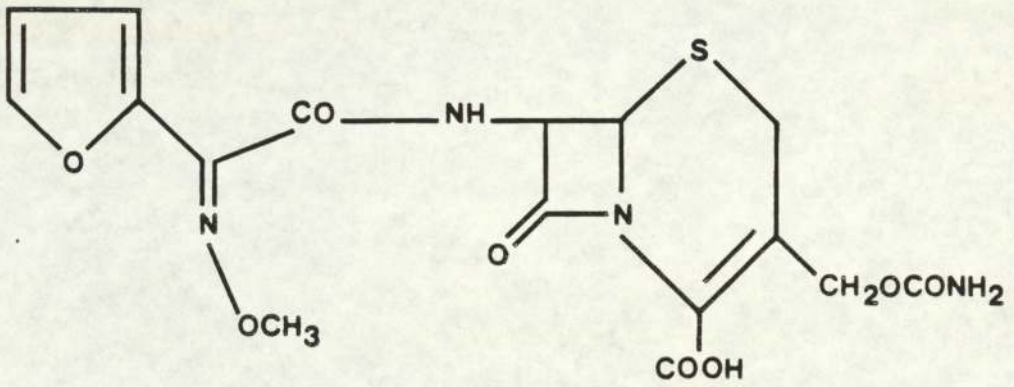
2.1.1 The Chemistry of Cefuroxime

Cefuroxime sodium is a white to faintly yellow crystalline powder with a molecular weight of 446.4. It is soluble in water at about 15% w/v, and sparingly soluble in methanol (1.3% w/v) and ethanol (0.1% w/v). The pH of a 10% solution is approximately pH 7, and a solution of between 5 and 6 percent is isotonic. In the dry state cefuroxime sodium is essentially stable and can be stored at room temperature. As

with other cephalosporins a slight yellowing of the powder may occur which is accelerated by light, temperature, humidity and the presence of oxygen.

At least 94% of the original concentration has been demonstrated to be present when cefuroxime sodium in Water for Injections is stored for 24 hours at 25°C, 5 hours at 30°C or 48 hours at 4°C. [93] The stability of cefuroxime

Figure 2.1.1 Structure of Cefuroxime



sodium in solutions containing a number of other drugs and parenteral fluids have also been investigated. These include lignocaine, hydrocortisone sodium phosphate, potassium chloride, cloxacillin, carbenicillin, heparin, dextrose 5% sodium lactate and sodium bicarbonate solutions. [94,95]

2.1.1.1 Analysis of Cefuroxime

Most groups measuring cefuroxime concentrations have been involved with investigating the concentration in tissues and body fluids and utilise biological assay methods. The most

common method used is a large plate agar diffusion technique with Bacillus subtilis the test organism. [82-85,96] Other groups use chromatographic techniques. [86,96] High performance liquid chromatography (HPLC) is specific, rapid and sensitive and can be used to separate the drug from prodrug or metabolites.

A number of techniques have been recorded for the separation of cefuroxime or cefuroxime axetil ester from blood samples either by serum protein precipitation [96] or reversed - phase extraction. [97] This type of technique has been developed to analyse a number of cephalosporins. The method of detection employed with both conventional and reversed - phase HPLC measurements is spectrophotometric monitoring in the ultraviolet wavelengths. Two wavelengths have been mentioned in the literature: 273nm [86,96] and 254nm. [97]

Three HPLC techniques for the analysis of cefuroxime in aqueous solutions have been described in the literature. [94,98]

Das Gupta and Stewart used two different columns and mobile phase combinations to analyse the stability of cefuroxime sodium in aqueous buffered solutions and intravenous admixtures. [94] Using a Microbondapak phenyl HPLC column, eluted with a mobile phase of 18.5% v/v methanol in water containing 0.02M ammonium acetate (pH 6.7), cefuroxime was noted to elute after cefuroxime degradation products. Using a Microbondapak C_{18} column, eluted with a mobile phase of 16% v/v methanol in water containing 0.01M each of ammonium acetate and potassium phosphate monobasic (pH 5.9) one of

the degradation products eluted after cefuroxime. Both methods used an ultraviolet detector set at 273nm. The mobile phase flow rate was 2.5ml/min for the Microbondapak phenyl column and 2.0ml/min for the Microbondapak C_{18} column. The results obtained when analysis was carried out using both systems were considered to be similar.

Coomber, Jefferies and Woodford developed an HPLC technique for the analysis of cefuroxime, and its separation from closely related compounds. [88] They investigated a number of column types and found that the use of a 5 micrometer Spherisorb C_8 column gave the most symmetrical peaks. A seamless stainless steel column (10cm x 4.5mm) was packed with 5 micrometer Spherisorb C_8. Detection was carried out at 273nm and an injection volume of 10 microlitres was used. The mobile phase consisted of 10% acetonitrile in 0.1M acetate buffer (pH 3.4), at a flow rate of 2ml/min. Orcinol monohydrate 1.5mg/ml aqueous solution was used as an internal standard.

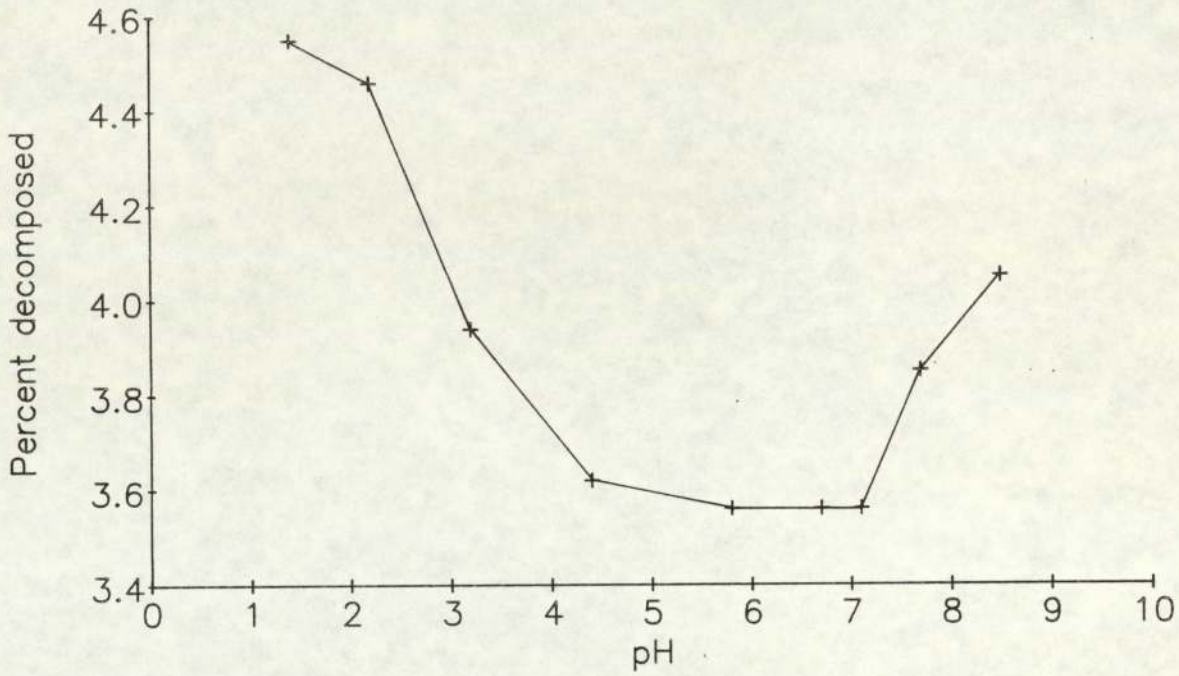
These authors described the ability of this technique to separate satisfactorily cefuroxime from a number of closely related compounds and that the results obtained compared favourably with those obtained using the Bacillus subtilis large plate microbiological assay method. It was also shown that chromatograms of degraded samples were free from peaks that would interfere with the peak obtained from the internal standard.

2.1.1.2 pH Profile

Das Gupta and Stewart have investigated the pH profile of a

number of cephalosporin antibiotics. The pH profile seen for cefuroxime was typical of cephalosporins, and showed an optimum pH range of stability between pH 4.5 and pH 7.3. [94]

Figure 2.1.2 - pH Profile of Cefuroxime



(Taken from Das Gupta & Steward, J Clin Hosp Pharm 1986,11,47) [94]

2.1.1.3 Mechanism of Degradation

Conners, Amidon and Kennon suggest that cephalosporins in solution follow a general scheme of decomposition. They suggest that at pH values of pH 3.5 or less, the beta-lactam ring undergoes hydrolysis and the products of this degradation usually have higher retention times than products of degradation at higher pH values which derive from hydrolysis of the side chain. [99]

2.1.2 The Composition of Artificial Tear Solutions

The role a drug vehicle plays in the ocular penetration of drugs depends on several factors. These include the

diffusion of the drug out of the vehicle and the length of time that the vehicle-drug combination is in contact with the eye after topical administration.

Hypromellose Eye drops BPC are the most commonly used artificial tears for the treatment of dry eyes. They are manufactured by a number of companies, but as they are prepared to British Pharmacopoeia specification the use of one product was felt to be representative of the others. Eight branded artificial tear solutions are commercially available in the UK. The viscosity agent used is either Hypromellose BPC , at concentrations between 0.25% and 1%, or polyvinyl alcohol 1.4%. In some products a second viscosity agent is present making the products more suitable for the treatment of certain types of dry eyes. Other compounds incorporated include dextran `70' and macrogol "8000".

In addition to the commercially available products preservative-free formulations exist for Hypromellose Eye Drops BPC and Sodium Chloride Eye Drops. It is usually necessary to manufacture these extemporaneously.

Vehicles of saline, methylcellulose, polyvinyl alcohol and white soft paraffin are frequently used in the preparation of ophthalmic drugs for topical use. Methylcellulose, polyvinyl alcohol and soft white paraffin have all been demonstrated to increase the contact time of the preparation with the eye and the penetration of drug. [18,90] Methylcellulose and polyvinyl alcohol can be included in eye

Table 2.1.1 - Composition of Artificial Tear Solutions

Artificial Tear Solution	Viscosity Agent	Preservative	Other Components
BJ6 Eye Drops (Thornton & Ross)	hypromellose 0.25%	chlorhexidine acetate 0.0075%	sodium chloride sodium bicarbonate polysorbate 80
BJ6 Eye Drops (Daniels)	hypromellose 0.3%	benzalkonium chloride 0.02%	sodium chloride sodium bicarbonate
Hypotears (Johnson & Johnson)	polyvinyl alcohol 1% macrogol `8000' 2%	benzalkonium chloride 0.01% disodium edetate 0.03%	"Lipiden" polymeric vehicle (+)
Hypromellose BPC (Daniels)	hypromellose 0.3%	benzalkonium chloride 0.01%	sodium chloride potassium chloride sodium borate boric acid
Hypromellose PF (SFMU)	hypromellose 0.3%	----	sodium chloride potassium chloride sodium borate boric acid
Isopto - Alkaline (Alcon)	hypromellose 1.0%	benzalkonium chloride 0.01%	sodium citrate sodium chloride sodium phosphate sodium biphosphate
Isopto - Plain (Alcon)	hypromellose 0.5%	benzalkonium chloride 0.01%	sodium citrate sodium chloride sodium phosphate sodium biphosphate
Liquifilm Tears (Allergan)	polyvinyl alcohol 1.4%	benzalkonium chloride 0.005% disodium edetate 0.015%	sodium chloride sodium phosphate sodium diphosphate
Sno Tears (Smith & Nephew)	polyvinyl alcohol 1.4% hydroxyethyl - cellulose	benzalkonium chloride 0.004% disodium edetate 0.02%	sodium chloride sodium hydroxide
Sodium Chloride (Daniels)	----	benzalkonium chloride 0.01%	sodium chloride
Sodium Chloride PF (SFMU)	----	----	sodium chloride
Tears Naturale (Alcon)	hypromellose 0.3% dextran `70' 0.1%	benzalkonium chloride 0.01% disodium edetate 0.05%	sodium chloride potassium chloride

(+ manufacturer unwilling to disclose other constituents)

drop formulations. Soft white paraffin is used in the preparation of ophthalmic ointments.

2.1.2.1. Viscosity Agents

Methylcellulose and hydroxypropylmethylcellose (hypromellose) are non-irritating and chemically inert colloids, which dissolve in water to produce a viscous, colourless solution having a high degree of transparency and a refractive index similar to that of the cornea. Such a solution is useful as a vehicle for ophthalmic medication, and as a substitute for natural secretions in cases of keratoconjunctivitis ("Dry Eyes"). Hypromellose, the hydroxypropyl derivative of methylcellulose, is now more commonly used than its parent compound. It has better solubility, its mucilages have greater clarity and contain fewer undispersed fibres and aqueous solutions are more tolerant to salts. It is used at a concentration of 0.25 - 1% in eye drop formulations. [92]

Polyvinyl alcohol, usually employed at a concentration of 1.4% w/v, in aqueous solution also offers an ophthalmic solution which does not blur vision and has good adhesive properties ensuring an increased contact time with the eye. Like the substituted cellulose ethers, it is soluble in water, its solutions are transparent and colourless, and may be sterilised by autoclaving. The main advantage of polyvinyl alcohol is that it has an excellent contact time on the eye despite the low viscosity of its solutions, and can easily be sterilised by terminal filtration through a 0.2 micron membrane, which is not possible for the

methycelluloses. Polyvinyl alcohol has also been shown to have no effect on the regeneration of corneal epithelial tissue as is seen with methylcellulose. Solutions of polyvinyl alcohol may thicken or gel if formulated in the presence of sodium bicarbonate, sodium borate or inorganic sulphates. [91]

Table 2.1.2 - Viscosity Values for Artificial Tear Solutions

Artificial Tear Solution (Manufacturer)	Viscosity (Centipoise)
BJ6 (Thornton & Ross)	8.5
BJ6 (Daniels)	7.0
Hypotears (Johnson & Johnson)	3.0
Hypromellose BP (Daniels)	9.0
Hypromellose PF (SFMU)	9.0
Isopto - Alkaline (Alcon)	308.5
Isopto - Plain (Alcon)	32.0
Liquifilm Tears (Allergan)	5.0
Sno Tears (Smith & Nephew)	25.0
Sodium Chloride BP (Daniels)	1.0
Sodium Chloride PF (SFMU)	1.0
Tears Naturale (Alcon)	10.5

SFMU = Sterile Fluids Manufacturing Unit. Queen Elizabeth Hospital, Birmingham
PF = Preservative Free

(Measured using a Brookfield Viscometer LVFD with 2nd spindle at 60 R.P.M.).

2.1.2.2. Preservatives

Benzalkonium chloride is a quaternary ammonium compound, and cationic surfactant, widely used as a preservative in the preparation of eye drops. For this purpose it is usually employed in a concentration of 0.01% w/v. It is bactericidal against a wide range of Gram-positive and some Gram-negative organisms. The antimicrobial activity is greatest at pH 8

and is reduced in acidic pH. The inclusion of disodium edetate in solutions containing benzalkonium chloride enhances the antibacterial effect, while it is decreased in the presence of hypromellose, calcium and potassium ions. Solutions containing 0.02% w/v benzalkonium chloride are usually well-tolerated by the eye, but concentrations above 0.1% w/v are irritant. The repeated application of benzalkonium chloride to the cornea can have deleterious effects on the corneal epithelium and tear film stability.[100]

Chlorhexidine acetate, the preservative present in BJ6 eye drops manufactured by Thornton & Ross is a cationic disinfectant active against many Gram-positive and some Gram-negative bacteria. It is most active at neutral or slightly alkaline pH, and its activity is reduced by the presence of organic matter, insoluble magnesium, zinc and calcium compounds and enhanced by the presence of disodium edetate. At the concentration usually employed in eye drop formulations (0.01% w/v) it is compatible with most anions other than sulphates.

All commercially available artificial tear solutions, with the exception of BJ6 eye drops (made by Thornton & Ross), contain benzalkonium chloride as the preservative. Until recently Liquifilm Tears was preserved with Chlorbutanol but the formulation has been changed.

2.1.2.3 Other Components

Other important factors to be considered in the preparation of an ophthalmic solution are tonicity, pH, stability,

preservative system and sterility.

The tonicity of the tear film is usually quoted as 0.9% w/v

Table 2.1.3. - Osmolarity Values for Artificial Tear Solutions

Artificial Tear Solution (Manufacturer)	Osmolarity (mOsm/L)
BJ6 (Thornton & Ross)	286
BJ6 (Daniels)	290
Hypotears (Johnson & Johnson)	224
Hypromellose BP (Daniels)	310
Hypromellose PF (SFMU)	296
Isopto - Alkaline (Alcon)	245
Isopto - Plain (Alcon)	241
Liquifilm Tears (Allergan)	238
Sno Tears (Smith & Nephew)	316
Sodium Chloride BP (Daniels)	286
Sodium Chloride PF (SFMU)	283
Tears Naturale (Alcon)	277

SFMU = Sterile Fluids Manufacturing Unit. Queen Elizabeth Hospital, Birmingham
PF = Preservative Free

(Measured using an Advanced Instruments Ltd Osmometer, which uses the principle of freezing point depression)

sodium chloride, although Potts infers that it is in fact slightly higher at 1.35% w/v sodium chloride. [14,101] In terms of osmolarity the figure usually refered to for serum and tears is 305 mOsm/litre. [102]

The eye can tolerate solutions having a range of equivalents from 0.6 - 2% w/v sodium chloride. It can be seen from Table 2.1.3. that all artificial tear solutions used in this study approximate to the tonicity of tears.

Simple compounds such as sodium bicarbonate and boric acid may be added to eye drop formulations to adjust the pH.

Buffers may be used to maintain the pH of the eye drops at an optimum, both for the stability of the drugs they contain and to ensure patient comfort. Examples of buffers used in ophthalmic preparations include: borate buffer (pH range 6.8 - 9.1), phosphate buffer (pH range 4.5 - 8.5) and citrate buffer (pH range 2.5 - 6.5).

The measured value of a number of the artificial tear solutions did not agree with that quoted by the manufacturer.

Table 2.1.4 - pH Values of Artificial Tear Solutions

Artificial Tear Solution (Manufacturer)	pH Quoted	pH Measured
BJ6 (Thornton & Ross)	8.0 - 9.0	8.40
BJ6 Daniels)	8.0 - 9.0	9.45
Hypotears (Johnson & Johnson)	approx. 7	5.87
Hypromellose BP (Daniels)	8.4 - 8.6	8.52
Hypromellose PF (SFMU)	8.45	8.46
Isopto - Alkaline (Alcon)	approx. 7	7.40
Isopto - Plain (Alcon)	approx. 7	7.41
Liquifilm Tears (Allergan)	6.0 - 7.5	6.77
Sno Tears (Smith & Nephew)	4.5 - 6.0	5.02
Sodium Chloride BP (Daniels)	5.8 - 6.5	6.29
Sodium Chloride PF (SFMU)	6.85	5.46
Tears Naturale (Alcon)	approx. 7	6.85

SFMU = Sterile Fluids Manufacturing Unit. Queen Elizabeth Hospital, Birmingham
PF = Preservative Free

2.2 METHODS

The stability of cefuroxime eye drops prepared in artificial tear solutions was investigated in 12 formulations.

The available artificial tear solutions vary widely in terms of pH and composition (see Tables 2.1.1 and 2.1.4). The objective of this investigation was to evaluate the stability of cefuroxime sodium in commercially available artificial tear solutions, in sodium chloride eye drops and sterile water for injection.

The effects of some of the individual components of the artificial tear solutions were also investigated. Preliminary observations from earlier work had suggested that benzalkonium chloride concentration and pH, which differ between the available products, may affect the stability of cefuroxime in these solutions. The effects of changing benzalkonium chloride and hypromellose concentration at pH 7.6 and of changing pH were investigated in phosphate buffer.

2.2.1 Materials and Equipment

2.2.1.1 Chemicals

Cefuroxime sodium was obtained as Zinacef Injection 250mg, 750mg or 1.5g vials, from Glaxo Laboratories, Greenford, Middlesex. Orcinol monohydrate powder was obtained from Sigma Chemical Company, Poole, Dorset. Artificial Tear Solutions were obtained via normal pharmaceutical wholesalers, and wherever possible were all of the same batch. Benzalkonium Chloride was obtained as a 10% solution from the Sterile Fluids Manufacturing Unit, Queen Elizabeth

Hospital, Birmingham.

2.2.1.2 Solvents

All solvents used were of Analar or HPLC grade, were obtained from BDH Chemicals, and used as obtained. Distilled Water was obtained from West Midlands Regional Sterile Production Unit (Parkfields).

2.2.1.3 Equipment

All glassware had undergone a thorough washing proceedure prior to use, which included rinsing with distilled water.

2.2.1.4 Measurements

All weighings were carried out using pre-weighed glass vessels, on a Mettler AJ100 four figure balance. All large volume pipettings were carried out using class A glass pipette of an appropriate volume. For volumes of 0.2ml a Gilson - Microman pipette was used.

2.2.2 Sample Preparation

2.2.2.1 Investigation of the Effect of Freezing Samples

In order to confirm the quenching action of storing samples obtained from the later parts of the study in the freezer at -18°C, the effect of freezer storage was investigated.

The solutions under examination were prepared by accurately weighing 10g of cefuroxime sodium (Zinacef, Glaxo Laboratories). This was dissolved in distilled water and made up to a volume of 200ml, from which 80 samples of 1ml were taken and stored in 1.5ml plastic microcentrifuge tubes. 30 were stored in the freezer at -18°C, and 30 in the fridge at 4°C. Twenty samples were analysed for cefuroxime

concentration on day 0. On days 28, 56 and 84, ten samples stored at -18°C and 10 samples stored at 4°C were withdrawn from storage and analysed for cefuroxime.

Students `t-test' was carried out on the results obtained. A statistically significant difference was taken to be P > 0.05 between those samples stored at -18°C and at 4°C, and between those stored at -18°C on days 0, 28, 56 and 84.

2.2.2.2 Qualitative Stability Investigation of Cefuroxime in Artificial Tear Solutions

Test formulations were prepared by accurately weighing 1.5g of cefuroxime sodium (Zinacef, Glaxo laboratories). This was dissolved in the solution under investigation and made up to a volume of 30ml. The solutions used were as follows:

BJ6 eye drops
Hypotears
Hypromellose Eye drops BPC
Hypromellose Preservative Free eye drops
Isopto - Alkaline
Isopto - Plain
Liquifilm Tears
Sno Tears
Sodium Chloride 0.9% eye drops
Sodium Chloride Preservative Free eye drops
Tears Naturale
Water (Distilled)

The theoretical drug concentration in the test formulations was 50mg/ml (5%) which is expected to be effective against micro-organisms sensitive to cefuroxime, and was identified in .the questionnaire in Part 1 as being commonly used. The solutions were stored in the dark in clear glass bijou bottles at 4°C. Each test formulation was visually inspected for turbidity and particles and checked for colour change and odour immediately after reconstitution and at 7, 14, 21

and 28 days. The pH was also measured at these times. Initially and at 14 and 28 days a sample was collected from each test formulation and stored at -18°C for chemical analysis.

The visual stability and pH readings were then repeated for each test formulation, with the solutions stored in both clear glass bijou bottles and plastic sterile sample bottles. These samples were stored at both 4°C and 25°C. Samples were collected for chemical analysis but only those preparations which remained pharmaceutically elegant during this storage period were analysed.

2.2.2.3 Investigation of the Effects of Benzalkonium Chloride and Hypromellose Concentration

Test solutions were prepared by accurately weighing 1.5g of cefuroxime sodium (Zinacef, Glaxo laboratories). This was dissolved in phosphate buffer at pH 7.6 containing either concentrations of the preservative Benzalkonium Chloride (Sterile Fluids Manufacturing Unit, Queen Elizabeth Hospital) in the range 0.0005% to 0.02% or Hypromellose BP in the range 0.1% to 1.0%. These were made up to a volume of 30ml. The theoretical drug concentration in the test formulations was 50mg/ml (5%). The solutions were stored in the dark in clear glass bijou bottles at 4°C. Each test solution was visually inspected for turbidity and particles, checked for colour change and odour and the pH measured immediately after reconstitution and at 7, 14, 21 and 28 days. No samples were taken for chemical analysis.

2.2.2.4 Investigation of the Effects of pH

Test solutions were prepared by accurately weighing 1.5g of cefuroxime sodium (Zinacef, Glaxo laboratories). This was dissolved in phosphate buffer of varying pH between 4.5 and 9.0 and made up to a volume of 30ml. The theoretical drug concentration in the test formulations was 50mg/ml (5%). The solutions were stored in the dark in clear glass bijou bottles at 4°C. Each test solution was visually inspected for turbidity and particles , checked for colour change and odour and the pH measured immediately after reconstitution and at 7, 14, 21 and 28 days. No samples were taken for chemical analysis.

2.2.2.5 Quantitative Stability Investigation of Cefuroxime in Artificial Tear Solutions

Those artificial tear solutions which appeared promising in the qualitative investigations were then studied on a long term quantitative basis. Cefuroxime sodium in Sno Tears, BJ6 and Hypromellose Preservative Free were prepared and investigated over a period of up to 6 months and at a number of temperatures. Cefuroxime sodium in water for injection was included as a comparison.

Four replicates of each of the four test formulations were prepared by accurately weighing 10g cefuroxime sodium (Zinacef, Glaxo Laboratories). This was dissolved in the solution under investigation and made up to a volume of 200ml. The theoretical drug concentration in the test formulations was 50mg/ml (5%). This was divided between 6 vials and stored in the dark at 4°C, 25°C, 32°C or 50°C. All samples were stored in plastic sterile sample containers as

used during the earlier experiments. Therefore at each of the four temperatures, twenty-four sample containers were stored, six of each of the four test formulations.

A 1ml sample was collected from each solution on days 0 to 4, 6, 7, 9, 12, 14, 16, 19, 21, 25 and 28 and at weekly intervals thereafter for three months. Three further samples were taken during months four to six for those solutions still under investigation. Where sample collection was not possible on the scheduled day, sampling was carried out on the nearest day possible and this was taken into account when the results were analysed. The pH was measured when a sample was taken. All samples were stored in plastic microcentrifuge tubes at -18oC for chemical analysis.

2.2.3 Analytical Technique

A high performance liquid chromatographic technique was used to assay the test formulations for cefuroxime concentration. The method used was adapted from that documented by Coomber, Jeffries and Woodford. [88] The acetonitrile content of the mobile phase was reduced from 10% to 7% to give equivalent separation to that reported and different dilution procedures were used for the sample and standard solutions to allow for a different injection volume.

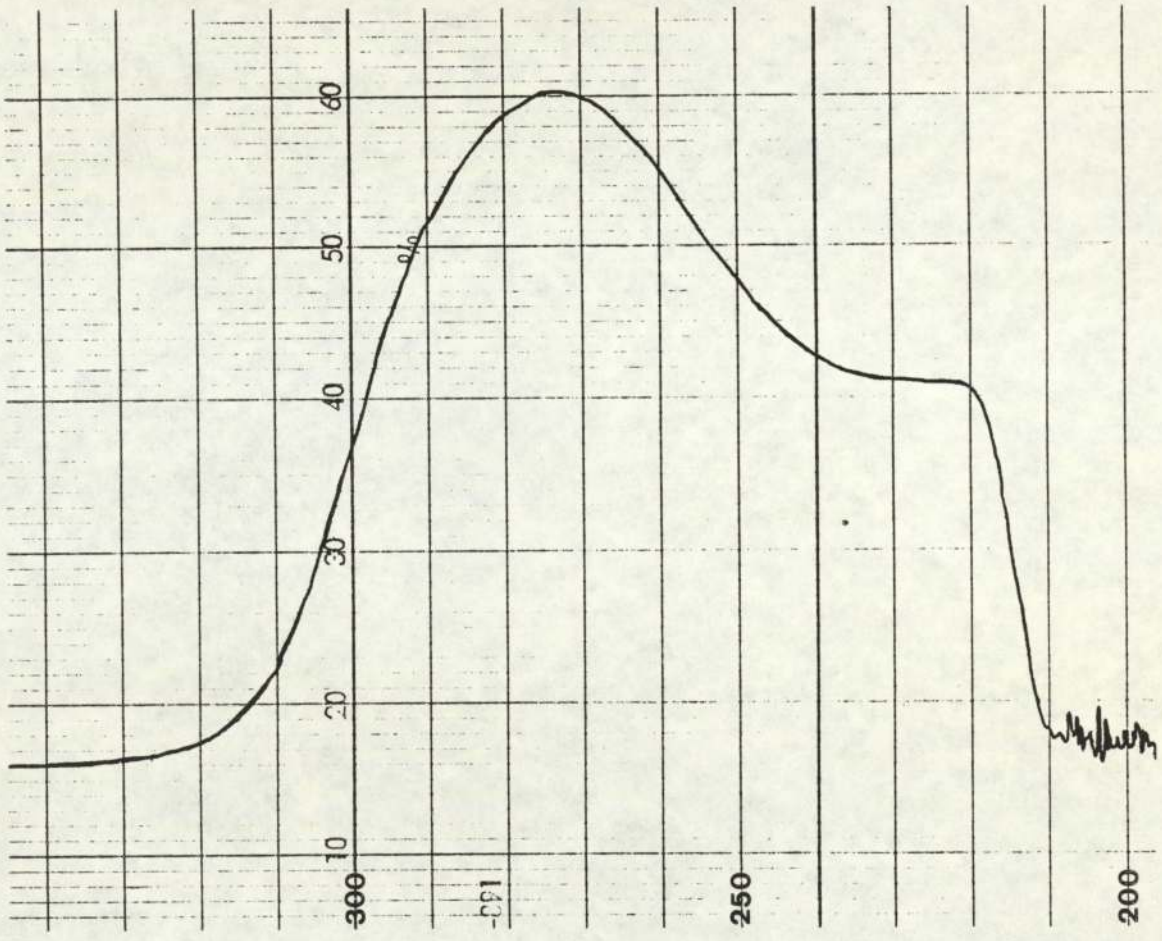
The equipment used consisted of a Cecil CE1100 liquid chromatography pump, Talbot ASI-4 Autosampler and Pye Unicam LC-UV variable wavelength detector. A 10cm Spherisorb 5 micrometer S5 Hexyl reversed phase column was eluted with a mobile phase of 7% acetonitrile in 0.1M acetate buffer of pH 3.4 +/- 0.2. All solvents were of HPLC grade. The mobile

phase was filtered through a Whatman 0.7 micrometer glass filter and degassed under a vacuum with agitation prior to use.

2.2.3.1 Confirmation of UV Spectra

The analytical technique used by Coomber, Jefferies and Woodford, [88] quoted the detection wavelength to be 273nm. To

Figure 2.2.1 - UV Spectra of Cefuroxime



confirm that this was indeed the wavelength of maximum absorption for cefuroxime and orcinol monohydrate the UV spectra of both compounds in mobile phase was measured using a Cecil 594 Double Beam Spectrophotometer.

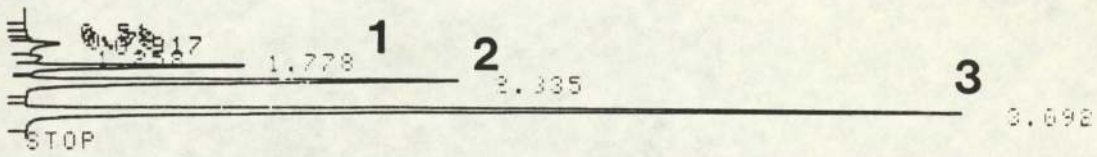
This was repeated for the artificial tear solutions under investigation to check for the presence of any absorption in

the area of the 273nm which may interfere with the results obtained using the HPLC. No interference was observed.

2.2.3.2 Analytical Parameters

Detection of cefuroxime was achieved at a wavelength of 273nm and 0.32 absorbance units full scale. An injection volume of 20 microlitres was used and peak areas were measured with a Shimadzu CR3A Chromatopac computing integrator. Orcinol monohydrate 1.5mg/ml aqueous solution was used as an internal standard. At a flow rate of 2ml/min cefuroxime sodium eluted with a retention time of 2.3 minutes and the internal standard had a retention time of 3.1 minutes. Cefuroxime degradation products were seen to elute from the column between 0.9 and 1.7 minutes. The cefuroxime to orcinol peak : area ratio was approximately 0.8.

Figure 2.2.2 - Chromatogram of Cefuroxime



Key : 1. Degradation products of cefuroxime
2. Cefuroxime
3. Orcinol

2.2.4 Preparation of Samples for Analysis

An accurately prepared solution of cefuroxime sodium in water containing approximately 50mg/ml was used to calculate

cefuroxime sodium content of the test formulations.

Both standard and sample solutions were prepared in the same way. Before analysis the test formulation samples were thawed by being allowed to reach room temperature. A 200ul aliquot, measured using a fixed volume Gilson Microman autopipette was added to 50ml of internal standard and diluted to 250ml with distilled water in a volumetric flask.

Once solvent flow and base line conditions were stabilised replicate injections of the standard solution were injected to ensure a reproducible cefuroxime to orcinol peak-area ratio. Duplicate injections were then made in the sequence standard, sample, sample, standard. The percentage of drug remaining was calculated by comparing peak-area ratio in each formulation with that of the standard solution.

2.2.5 Calibration

2.2.5.1 Coefficient of Correlation

The assay method was investigated to ensure linearity of the cefuroxime : orcinol peak-area ratio to corresponding concentrations of cefuroxime. Samples of cefuroxime at concentrations between 0.1mg/ml and 1mg/ml were assayed.

Table 2.2.1 - Variation of Response to Cefuroxime Concentration

Cefuroxime Concentration (mg/ml)	Response
0.1	0.10
0.2	0.19
0.4	0.43
0.6	0.56
0.8	0.74
1.0	0.97

These are representative of the range of concentrations expected to be encountered during the degradation of cefuroxime eye drops, and following the dilution stage carried out to enable HPLC analysis. It can be seen from Table 2.2.1 that the response obtained is linear. A graph of peak-area ratio versus cefuroxime concentration has a straight line with a correlation coefficient of 0.9972, the intercept at zero cefuroxime concentration is small (+0.012). Recovery of the added cefuroxime was seen to be 100%.

2.2.5.2 Coefficient of Variation

A solution containing approximately 1mg/ml was prepared. To determine the reproducibility of the assay method 6 samples were taken and independently diluted. They were then analysed by the HPLC method described. The response of each sample is expressed in terms of the ratio of cefuroxime peak-area to orcinol peak-area.

Table 2.2.2 - Variation in Response to the same Cefuroxime Concentration

Sample Number	Response
1	0.5608
2	0.5633
3	0.5605
4	0.5599
5	0.5606
6	0.5623

This gave an average response of 0.5612 with a standard deviation of 1.29×10^{-3}. A coefficient of variation was calculated as 0.23% at a concentration typical of the eye drops being investigated.

2.2.6 Preservative Testing

The British Pharmacopeia dictates a testing procedure intended as a means by which the efficacy of the preservative system included in a formulated product may be assessed. The purpose of a preservative system is to prevent adverse effects arising from microbial contamination subsequent to manufacture.

The organisms specified for use in the testing procedure are intended to be representative of those that might be expected to be found in the enviroment in which the preparation is manufactured, stored and used.

The test period should extend over at least twenty eight days, and the organisms suggested for use are Candida albicans, Aspergillus niger, Pseudomonas aeruginosa and Staphylococcus aureus.

2.2.6.1 Testing Procedure

It was decided to carry out the BP preservative testing procedure only on the product identified from the qualitative and quantitative stability studies of cefuroxime in artificial tear solutions as being the most promising.

Testing was carried out using the method specified in Appendix XVIC (1980) pA192 Part C of the British Pharmacopeia. The test organisms considered to be representative for ophthalmic products were Candida albicans, Pseudomonas aeruginosa and Staphylococcus aureus. Controls were prepared in 0.1% peptone water.

Colony counts were carried out at 0, 6 and 24 hours, and 7,

14 and 28 days. Plating out of colonies was carried out as follows:

Candida albicans	Sabourand's Agar
Staphylococcus aureus	Brain Heart Infusion Agar
Pseudomonas aeruginosa	Nutrient Agar

2.2.6.2 Interpretation of Results

For ophthalmic preparations intended for use on more than one occasion the following results must be obtained for the efficacy of the preservative system to be considered adequate.

For bacteria the number of organisms recovered per ml must be reduced by a factor of not less than 10^3 within 6 hours of challenge, and no organisms must be recovered at 24 hours and thereafter.

For moulds and yeasts the number of organisms recovered per ml must be reduced by a factor of not less than 10^2 within 7 days of challenge and there be no increase thereafter.

2.3 RESULTS

2.3.1 Freezer Stability Studies

Following analysis for cefuroxime concentration on day zero, the solution used for this study was show to contain 54.02mg/ml. Ten replicate samples were analysed at each temperature after each time period. The figures in Table 2.3.1 are expressed as the mean of ten samples, with standard deviation in brackets.

Table 2.3.1 - Cefuroxime Concentration Following Storage at -18°C and 4°C for Three Months

Time (days)	Cefuroxime Concentration -18°C	4°C
0	54.02 (0.46)	54.02 (0.46)
28	54.36 (0.49)	50.25 (0.36)
56	54.80 (0.43)	45.81 (0.95)
84	54.40 (0.15)	44.16 (0.36)

the samples stored at -18°C and those at 4°C on days 28, 56 and 84. The difference between samples stored at -18°C and those stored at 4°C was found to be very highly significant at each time period. ($0.001 > p$)

Students 't-test' showed there to be no significant difference between the samples stored at -18°C on days 0, 28, 56 and 84. ($0.5 > p > 0.1$)

2.3.2. Qualitative Stability Studies

2.3.2.1 Samples Stored in Glass Bijou Bottles at 4°C

Four test formulations demonstrated a colour change from pale yellow to bright yellow by day 7. These corresponded with those artificial tear solutions of pH 8.0 and above.

All solutions showed a slight discoloration by day 28, but did not reach bright yellow.

On preparation turbidity was seen in all test formulations, except one, prepared with artificial tear solutions containing benzalkonium chloride as preservative. The exception was Sno Tears which contains the lowest concentration of benzalkonium chloride at 0.004%.

Table 2.3.2 - Physicial Stability of Cefuroxime in Artificial Tear Solution stored in Glass at 4°C

Artificial Tear Solution	Day	Colour Change 0	7	14	21	28	Turbidity/precipitate 0	7	14	21	28
BJ6 (Thornton & Ross)		-	+	+	+	+	-	-	-	-	-
BJ6 (Daniels)		+	+	+	+	+	+	+	+	+	+
Hypotears		-	-	-	-	-	+	++	++	++	++
Hypromellose BP		+	+	+	+	+	+	+	++	++	++
Hypromellose Pres. Free		+	+	+	+	+	-	-	-	-	-
Isopto - Alkaline		-	-	-	-	-	+	+	+	+	+
Isopto - Plain		-	-	-	-	-	+	+	+	++	++
Liquifilm Tears		-	-	-	-	-	+	+	+	+	++
Sno Tears		-	-	-	-	-	-	-	-	-	-
Sodium Chloride BP		-	-	-	-	-	+	++	++	++	++
Sodium Chloride Pres. Free		-	-	-	-	-	-	-	-	-	-
Tears Naturale		-	-	-	-	-	+	+	++	++	++

+ = turbidity
++ = precipitate

BJ6 manufactured by Thornton & Ross, containing chlorhexidine acetate as preservative, and those preservative free solutions remained clear on preparation. By day 28 turbidity or a precipitate were present in all solutions which had shown turbidity on preparation. All other solutions remained clear throughout the investigation period.

The only test formulation to develop any sort of odour

during the test period was that prepared in Hypotears.

No appreciable change in pH was seen in most of the test formulations after 7 days. However those formulation which were initially acidic; Sno Tears and Hypotears showed the largest change in pH, becoming approximately neutral by day seven. This might be attributable to leaching of alkali from the glass bijou bottles.

Table 2.3.3 - pH Changes of Cefuroxime in Artificial Tear Solutions stored in Glass at 4°C

Artificial Tear Solution	Day	pH 0	7	14	28
BJ6 (Thornton & Ross)		8.34	8.12	8.02	7.98
BJ6 (Daniels)		9.25	8.89	8.60	8.34
Hypotears		5.93	6.89	7.26	7.35
Hypromellose BP		8.55	8.48	8.43	8.37
Hypromellose Pres. Free		8.48	8.42	8.36	8.23
Isopto - Alkaline		7.38	7.52	7.50	7.50
Isopto - Plain		7.38	7.50	7.47	7.47
Liquifilm Tears		6.76	6.83	6.88	6.83
Sno Tears		5.45	6.42	6.73	6.95
Sodium Chloride BP		7.02	7.02	7.14	7.15
Sodium Chloride Pres. Free		6.97	7.02	7.14	7.16
Tears Naturale		6.97	7.08	7.14	7.22

By day 28 all preparations which were initially acidic or neutral were within the pH range 7.3 - 7.5. Those formulations which were initially alkaline; Hypromellose, Hypromellose Preservative free and BJ6 remained alkaline.

Chemical analysis of the cefuroxime concentration present in each test formulation at days 0, 14 and 28 showed initial concentrations between 49.17mg/ml and 52.70mg/ml. All solutions were prepared as nominal 50mg/ml solutions.

At day 14 the cefuroxime concentration remaining ranged from 98.09% to 84.62%, and at day 28 from 95.84% to

83.34%. These figures are expressed in Table 2.3.4 as the mean of 3 replicated and the standard deviation (in brackets).

Table 2.3.4 - Stability of Cefuroxime Sodium at 4°C

Artificial Tear Solution	Initial Concentration (mg/ml)	Percentage of Initial Concentration Day 14	Day 28
BJ6 (Thornton & Ross)	50.18	96.60 (6.03)	95.20 (3.96)
BJ6 (Daniels)	-	-	-
Hypotears	49.67	98.09 (3.62)	89.89 (2.49)
Hypromellose BP	50.30	93.10 (4.73)	88.84 (5.85)
Hypromellose Pres. Free	49.75	95.19 (2.20)	87.84 (2.77)
Isopto - Alkaline	49.17	89.32 (1.11)	83.34 (6.28)
Isopto - Plain	50.23	96.54 (2.86)	95.84 (4.24)
Liquifilm Tears	49.91	94.91 (2.48)	89.20 (1.58)
Sno Tears	52.70	95.10 (4.30)	92.76 (1.41)
Sodium Chloride BP	51.38	84.62 (6.34)	85.27 (5.96)
Sodium Chloride Pres. Free	49.60	96.92 (1.80)	88.97 (2.70)
Tears Naturale	49.80	96.79 (1.44)	93.07 (1.04)
Water For Injections	50.00	96.96 (0.30)	93.34 (2.78)

2.3.2.2 Samples Stored in Plastic Containers at 4°C

When stored in plastic containers the same four test formulations demonstrated a colour change from pale yellow to bright yellow by day 7. Again all solutions showed a slight discolouration by day 28.

Table 2.3.5 - Physical Stability of Cefuroxime in Artificial Tear Solutions stored in Plastic at 4°C

Artificial Tear Solution	Colour Change Day 0	7	14	21	28	turbidity/precipitate 0	7	14	21	28
BJ6 (Thornton & Ross)	-	+	+	+	+	-	-	-	-	-
BJ6 (Daniels)	+	+	+	+	+	+	+	+	+	+
Hypotears	-	-	-	-	-	+	++	++	++	++
Hypromellose BP	+	+	+	+	+	+	+	++	++	++
Hypromellose Pres. Free	+	+	+	+	+	-	-	-	-	-
Isopto - Alkaline	-	-	-	-	-	+	+	+	+	+
Isopto - Plain	-	-	-	-	-	+	+	+	++	++
Liquifilm Tears	-	-	-	-	-	+	+	+	++	++
Sno Tears	-	-	-	-	-	-	-	-	-	-
Sodium Chloride BP	-	-	-	-	-	+	++	++	++	++
Sodium Chloride Pres. Free	-	-	-	-	-	-	-	-	-	-
Tears Naturale	-	-	-	-	-	+	+	++	++	++

+ = turbidity
++ = precipitate

The turbidity and precipitates see in solutions both immediately after reconstitution and by day 28 were seen in both glass and plastic containers. The only difference was that the precipitate seen in the Liquifilm Tears formulation was present in the plastic container by day 21, but not seen in glass until 28 days. The same solutions were observed as remaining clear.

When stored in a plastic container the Hypotears preparation did not show any development of odour.

Table 2.3.6 - pH Changes of Cefuroxime in Artificial Tear Solutions stored in Plastic at 4°C

Artificial Tear Solution	Day	pH 0	7	14	28
BJ6 (Thornton & Ross)		8.34	8.20	8.14	8.07
BJ6 (Daniels)		9.25	8.89	8.60	8.38
Hypotears		5.93	7.03	7.27	7.36
Hypromellose BP		8.55	8.50	8.42	8.36
Hypromellose Pres. Free		8.48	8.42	8.35	8.24
Isopto - Alkaline		7.38	7.49	7.45	7.49
Isopto - Plain		7.38	7.47	7.45	7.47
Liquifilm Tears		6.76	6.83	6.87	6.86
Sno Tears		5.45	6.51	6.92	7.08
Sodium Chloride BP		7.02	7.16	7.31	7.32
Sodium Chloride Pres. Free		6.97	7.15	7.29	7.33
Tears Naturale		6.97	7.16	7.31	7.35

Storing the test formulations in plastic containers did not appear to affect the trends seen with pH in the earlier samples stored in glass bottles. Again Sno Tears and Hypotears showed the largest changes in pH, and those solutions which were initially alkaline remained so.

Sodium Chloride BP, Sodium Chloride Preservative free and Tears Naturale showed the largest variation between the pH values recorded in solutions stored in glass bijou bottles and plastic specimen containers.

2.3.2.3 Samples Stored in Glass Bijou Bottles at 25°C

Three solutions were bright yellow immediately after preparation, while nine test formulations demonstrated a colour change to bright yellow by day 7. Those solutions which had changed from pale yellow to bright yellow when stored at 4°C developed a bright orange colour when stored at 25°C. All solutions showed discoloration to an orange colour by day 28.

With one exception turbidity was seen in all test formulations prepared with artificial tear solutions and in solutions containing benzalkonium chloride as preservative. The exception was Sno Tears which contains the lowest concentration of benzalkonium chloride at 0.004%. By day 7 the Sno Tears preparation also showed turbidity, and by day 28 only Isopto - Alkaline showed turbidity as opposed to a precipitate.

Table 2.3.7 - Physical Stability of Cefuroxime in Artificial Tear Solutions stored in Glass at 25°C

	Colour Change					turbidity/precipitate				
Artificial Tear Solution Day	0	7	14	21	28	0	7	14	21	28
BJ6 (Thornton & Ross)	-	+	+	+	+	-	-	-	-	-
BJ6 (Daniels)	+	++	++	++	++	+	++	++	++	++
Hypotears	-	+	+	+	++	+	++	++	++	++
Hypromellose BP	+	++	++	++	++	+	++	++	++	++
Hypromellose Pres. Free	+	++	++	++	++	-	-	-	-	-
Isopto - Alkaline	-	+	+	+	++	+	+	+	+	+
Isopto - Plain	-	+	+	+	++	+	++	++	++	++
Liquifilm Tears	-	+	+	+	+	+	++	++	++	++
Sno Tears	-	+	+	+	+	-	+	+	++	++
Sodium Chloride BP	-	+	+	+	+	+	++	++	++	++
Sodium Chloride Pres. Free	-	+	+	+	+	-	-	-	-	-
Tears Naturale	-	+	+	+	++	+	++	++	++	++
	+ = bright yellow ++ = orange					+ = turbidity ++ = precipitate				

Four solutions remained clear throughout the test period. BJ6 manufactured by Thornton & Ross, containing chlorhexidine acetate as preservative, and those preservative free solutions remained clear on preparation.

By day 28 all test formulations had developed some sort of odour.

Table 2.3.8 - pH Changes of Cefuroxime in Artificial Tear Solutions stored in Glass at 25°C

Artificial Tear Solution	Day	pH 0	7	14	28
BJ6 (Thornton & Ross)		8.34	7.46	7.30	7.22
BJ6 (Daniels)		9.25	7.97	7.58	7.41
Hypotears		5.93	7.35	7.25	7.15
Hypromellose BP		8.55	7.56	7.36	7.23
Hypromellose Pres. Free		8.48	7.52	7.31	7.19
Isopto - Alkaline		7.38	7.45	7.28	7.26
Isopto - Plain		7.38	7.41	7.28	7.24
Liquifilm Tears		6.76	7.17	7.08	7.11
Sno Tears		5.45	7.13	7.09	7.09
Sodium Chloride BP		7.02	7.42	7.38	7.34
Sodium Chloride Pres. Free		6.97	7.42	7.38	7.34
Tears Naturale		6.97	7.27	7.16	7.15

By day 7 all test formulations showed appreciable changes in pH. Whether the original pH had been acidic, neutral or alkaline all solutions were of within the range 7.0 - 8.0 by day 7 and between 7.0 and 7.5 by day 28.

2.3.2.4 Samples Stored in Plastic Containers at 25°C

The same colour changes from pale to bright yellow and orange were seen in plastic container stored at 25°C as were seen with solutions stored in glass containers. All solutions showed discoloration to an orange colour by day 28.

The same degree of turbidity and precipitation was seen in

the plastic stored solutions, with Sno Tears again showing turbidity and precipitate formation at 25°C, which was not seen at 4°C.

Table 2.3.9 - Physical Stability of Cefuroxime in Artificial Tear Solutions stored in Plastic at 25°C

Artificial Tear Solution	Day	Colour Change 0	7	14	21	28	turbidity/precipitate 0	7	14	21	28
BJ6 (Thornton & Ross)		-	+	+	+	+	-	-	-	-	-
BJ6 (Daniels)		+	++	++	++	++	+	++	++	++	++
Hypotears		-	+	+	+	++	+	++	++	++	++
Hypromellose BP		+	++	++	++	++	+	++	++	++	++
Hypromellose Pres. Free		+	++	++	++	++	-	-	-	-	-
Isopto - Alkaline		-	+	+	+	++	+	+	+	+	+
Isopto - Plain		-	+	+	+	++	+	++	++	++	++
Liquifilm Tears		-	+	+	+	+	+	++	++	++	++
Sno Tears		-	+	+	+	+	-	+	+	++	++
Sodium Chloride BP		-	+	+	+	+	+	++	++	++	++
Sodium Chloride Pres. Free		-	+	+	+	+	-	-	-	-	-
Tears Naturale		-	+	+	+	++	+	++	++	++	++
		+ = bright yellow					+ = turbidity				
		++ = orange					++ = precipitate				

Again four solutions remained clear throughout the test period, and by day 28 all test formulations had developed some sort of odour.

Table 2.3.10 - pH Changes of Cefuroxime in Artificial Tear Solutions stored in Plastic at 25°C

Artificial Tear Solution	Day	pH 0	7	14	28
BJ6 (Thornton & Ross)		8.34	7.52	7.43	7.52
BJ6 (Daniels)		9.25	7.59	7.56	7.54
Hypotears		5.93	7.41	7.36	7.40
Hypromellose BP		8.55	7.60	7.42	7.46
Hypromellose Pres. Free		8.48	7.59	7.40	7.45
Isopto - Alkaline		7.38	7.43	7.37	7.48
Isopto - Plain		7.38	7.44	7.37	7.43
Liquifilm Tears		6.76	7.20	7.23	7.34
Sno Tears		5.45	7.33	7.24	7.34
Sodium Chloride BP		7.02	7.49	7.47	7.53
Sodium Chloride Pres. Free		6.97	7.29	7.27	7.34
Tears Naturale		6.97	7.31	7.25	7.36

By day 7 all test formulations showed appreciable changes in pH. Whether the original pH had been acidic, neutral or alkaline all solutions were of within the range 7.2 - 7.6 by day 7 and between 7.3 and 7.5 by day 28. This is similar to the pH changes seen in solutions stored in glass at 25°C.

Of the samples repeated at 4°C and 25°C stored in glass and plastic, only those which did not show turbidity or the development of a precipitate were analysed for cefuroxime concentration. Three artificial tear test formulations fell into this category; Sno Tears, Hypromellose Preservative Free and BJ6 (Thornton & Ross). The solution prepared in Water for Injection was also included for comparison.

Table 2.3.11 - Stability of Cefuroxime at 4°C and 25°C Stored in Glass and Plastic Containers

Artificial Tear Solutions	Initial Concentration (mg/ml)	Percentage of Initial Concentration Day 14	Day 28
Stored in Glass at 4°C			
BJ6 (Thornton & Ross)	50.18	96.60 (6.03)	85.20 (3.86)
Hypromellose Pres. Free	49.75	95.19 (2.20)	87.84 (2.77)
Sno Tears	52.70	95.10 (4.30)	92.76 (1.41)
Water For Injections	50.00	96.96 (0.30)	93.34 (2.78)
Stored in Plastic at 4°C			
BJ6 (Thornton & Ross)	50.50	94.19 (0.38)	89.95 (1.52)
Hypromellose Pres. Free	50.78	94.11 (0.97)	91.04 (0.45)
Sno Tears	50.10	97.02 (0.46)	91.28 (0.40)
Water For Injections	50.63	96.66 (0.43)	93.24 (0.54)
Stored in Glass at 25°C			
BJ6 (Thornton & Ross)	50.93	26.72 (0.93)	5.43 (0.49)
Hypromellose Pres. Free	50.95	24.14 (1.04)	6.12 (0.45)
Sno Tears	50.11	31.94 (0.84)	8.79 (0.86)
Water For Injections	50.03	30.34 (0.29)	7.45 (0.98)
Stored in Plastic at 25°C			
BJ6 (Thornton & Ross)	50.54	25.16 (0.81)	4.91 (0.21)
Hypromellose Pres. Free	50.75	26.03 (0.29)	5.61 (0.86)
Sno Tears	50.14	32.71 (0.79)	7.63 (0.92)
Water For Injections	50.03	29.10 (2.61)	7.23 (0.64)

Table 2.3.11 shows the cefuroxime concentration found in test formulations analysed in triplicate. The standard deviation is shown in brackets.

Students `t-test' ($0.5 > p > 0.1$) showed there to be no significant differences between the concentrations of cefuroxime remaining at days 14 or 28 when samples were stored in glass bijou bottles or in plastic specimen containers, at either 4°C or 25°C.

2.3.3 Effect of Benzalkonium Chloride and Hypromellose Concentration

Those solutions containing varying concentrations of benzalkonium and hypromellose showed no colour change during the 28 day period. All solutions remained pale yellow.

Despite being prepared in phosphate buffer at pH 7.6, by day 28 all solutions had a pH value of approximately 7.5. The change seen in pH was slower with the samples containing benzalkonium chloride, which did not approximate to pH 7.5 until day 21. The hypromellose containing solutions reached a pH of approximately 7.5 by day 7.

All solutions containing hypromellose remained clear during the 28 day period. Of those containing benzalkonium chloride only those samples containing a concentration of 0.002% or less remained clear throughout.

Those samples containing 0.006% or more benzalkonium chloride showed turbidity immediately upon preparation and by day 7 contained a precipitate. The sample containing 0.004% which was clear on preparation, and the sample

containing 0.005% which showed turbidity on preparation had both developed a precipitate by day 7.

The sample containing 0.003% benzalkonium chloride was clear on preparation, had developed turbidity by day 7 and showed a precipitate by day 21.

Table 2.3.12 - Physical Stability of Cefuroxime in Benzalkonium Solution or Hypromellose

Solution Composition	Day	turbidity/precipitate 0	7	14	21	28
Benzalkonium Chloride		-	-	-	-	-
0.0005%		-	-	-	-	-
0.001%		-	-	-	-	-
0.002%		-	+	+	++	++
0.003%		-	++	++	++	++
0.004%		+	++	++	++	++
0.005%		+	++	++	++	++
0.006%		+	++	++	++	++
0.007%		+	++	++	++	++
0.008%		+	++	++	++	++
0.009%		+	++	++	++	++
0.01%		+	++	++	++	++
0.02%		+	++	++	++	++
Hypromellose						
0.1%		-	-	-	-	-
0.2%		-	-	-	-	-
0.3%		-	-	-	-	-
0.4%		-	-	-	-	-
0.5%		-	-	-	-	-
1.0%		-	-	-	-	-

+ = turbidity
++ = precipitate

The cefuroxime solutions prepared in phosphate buffer containing varying concentrations of hypromellose showed no visual changes during the 28 day period, remaining clear pale yellow solutions.

2.3.4 Effect of pH Variation

Samples containing 5% cefuroxime in phosphate buffer were prepared over the pH range 4.5 to 9.0. This involved 21

samples, at pH 4.5, 5.0, 5.2, 5.4, 5.6, 5.8, 6.0, 6.2, 6.4, 6.6, 6.8, 7.0, 7.2, 7.4, 7.6, 7.8, 8.0, 8.2, 8.4, 8.6, 9.0.

Immediately after preparation all solutions were clear and pale yellow. During the 28 day period, no solutions developed turbidity, precipitation or odour, and the pH showed no appreciable change.

By day 7 those samples at pH 7.2 and above had changed colour from a pale yellow to a brighter yellow. Those solutions above pH 8.0 developed a very bright yellow colour. Over the 28 day period all samples showed some discoloration, but the spectrum of colour from pale yellow in acidic solutions to very bright yellow in alkaline solutions was consistent.

2.3.5 Quantitative Stability Studies

Those test formulations identified as promising from the qualitative stability studies were considered to be Sno Tears, Hypromellose Preservative Free eye drops, and BJ6 eye drops (Thornton & Ross). Cefuroxime was also prepared for analysis in Distilled Water as a comparison. All sample solutions prepared were nominally 50mg/ml (5%).

Following the initial analysis of samples stored at 50°C, these were excluded from the rest of the study as degradation appeared to occur too rapidly to ensure accurate results with a sampling period of 24 hours. Those samples stored at 50°C also appeared to have developed a crust around the cap of the containers, which was felt likely to make any analysis inaccurate.

Students `t-test' performed on each set of results confirmed that all sets of data were from a single population. There was no significant difference seen between any of the samples of each test formulation (0.5 > p).

Graphical representation of the results obtained was plotted in the form Concentration versus Time. This gave a non linear plot, which correlated closely to an exponential curve in each case. The exponential nature of the curves obtained indicates that the degradation of cefuroxime in the artificial tear solutions investigated is first order.

Plotting the results as Log Concentration versus Time gave a linear graph, confirming the first order nature of the reaction.

The degradation of cefuroxime sodium in BJ6 Eye Drops, Sno Tears, Hypromellose Preservative Free Eye Drops and Distilled Water follows first order kinetics. The stability parameters are shown in Table 2.3.17.

Table 2.3.13 Stability Parameters of Cefuroxime Degradation

Formulation	Degradation Constant (%/day) 4°C	25°C	32°C
BJ6 Eye Drops	0.0037	0.1046	0.1680
Hypromellose PF	0.0034	0.0998	0.1788
Sno Tears	0.0026	0.0842	0.1708
Distilled Water	0.0027	0.0894	0.1724

All cefuroxime concentrations are the mean of three replicate samples. (The standard deviation appears in

brackets).

Table 2.3.14 - Stability of Cefuroxime Sodium in BJ6 Eye Drops

Day	Percentage of Nominal Concentration Remaining 4°C		25°C		32°C	
0	100.99	(0.19)	91.21	(0.35)	103.08	(3.37)
1	99.48	(0.56)	84.20	(0.24)	88.48	(3.21)
2	98.53	(0.77)	78.44	(1.70)	73.56	(2.23)
3	99.12	(0.57)	69.11	(0.43)	61.58	(1.58)
4	98.85	(0.17)	61.18	(3.15)	52.54	(0.56)
6	98.03	(0.59)	54.13	(2.50)	37.94	(0.66)
7	97.77	(0.42)	49.59	(2.38)	31.24	(0.20)
9	97.29	(1.03)	40.74	(1.99)	20.99	(0.34)
11					14.39	(0.87)
12	95.53	(1.24)	31.24	(0.95)		
14	94.19	(0.38)	25.16	(0.81)	8.47	(0.29)
16	94.75	(1.23)	19.90	(0.37)	5.51	(0.76)
19	92.29	(0.88)	14.61	(0.46)		
21	92.03	(0.83)	12.32	(0.39)		
23					2.69	(0.39)
25	90.68	(1.49)	7.59	(0.58)		
29	89.95	(1.52)	4.91	(0.21)		
35	88.70	(1.17)	2.03	(0.25)		
42	86.71	(0.96)				
49	83.56	(1.09)				
56	81.84	(0.97)				
63	79.29	(1.76)				
72	77.08	(0.30)				
77	75.49	(1.15)				
85	73.81	(2.01)				
126	62.34	(0.54)				
134	61.25	(0.47)				

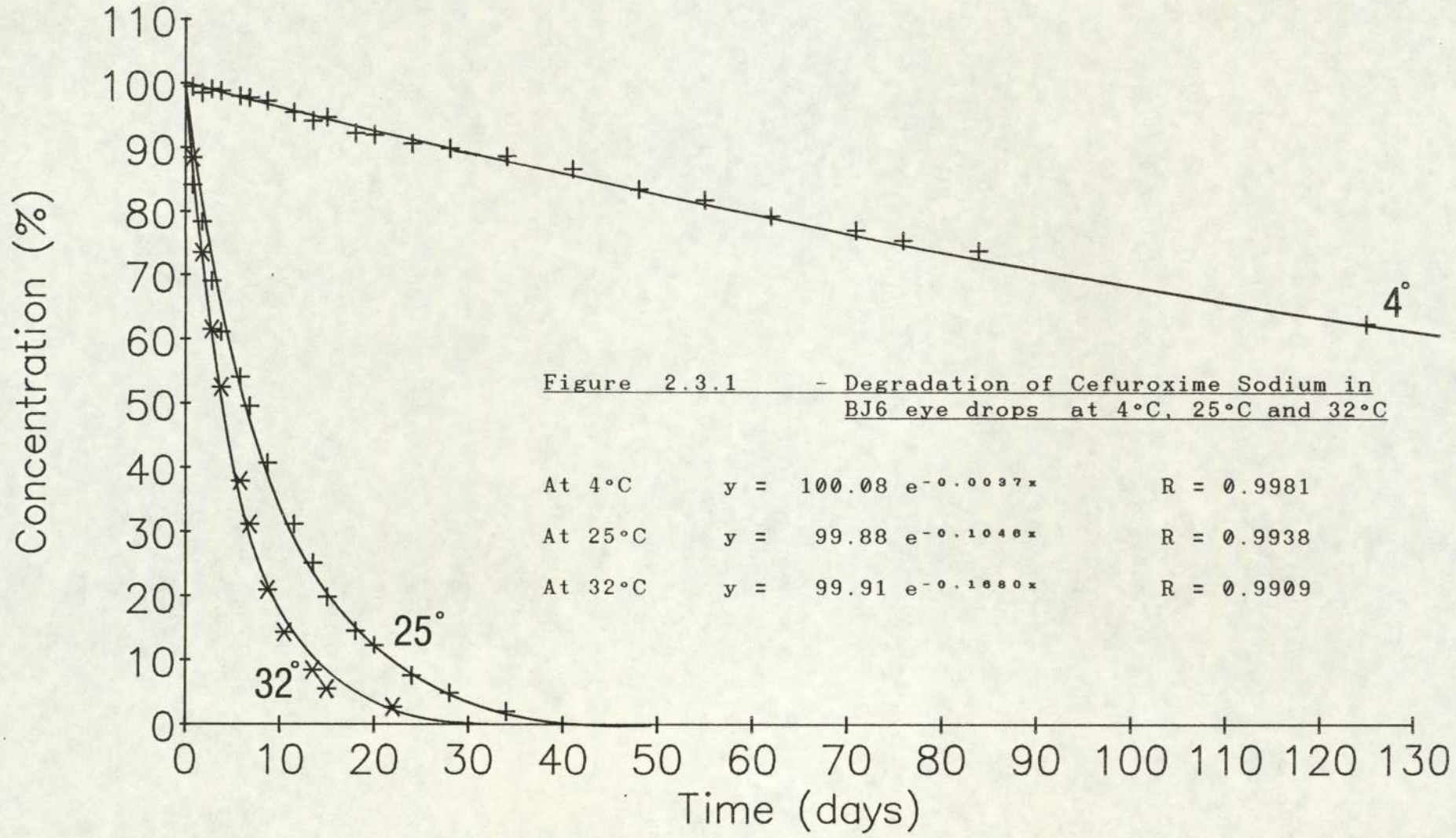


Figure 2.3.1 - Degradation of Cefuroxime Sodium in BJ6 eye drops at 4°C, 25°C and 32°C

At 4°C	$y = 100.08\ e^{-0.0037x}$	R = 0.9981
At 25°C	$y = 99.88\ e^{-0.1046x}$	R = 0.9938
At 32°C	$y = 99.91\ e^{-0.1680x}$	R = 0.9909

Figure 2.3.2 - Degradation of Cefuroxime Sodium in BJ6 eye drops at 4°C, 25°C and 32°C (Logarithmic Plot)

At 4°C	y = -0.0016x + 2.000	R = 0.9991
At 25°C	y = -0.0454x + 2.000	R = 0.9969
At 32°C	y = -0.0738x + 1.993	R = 0.9897

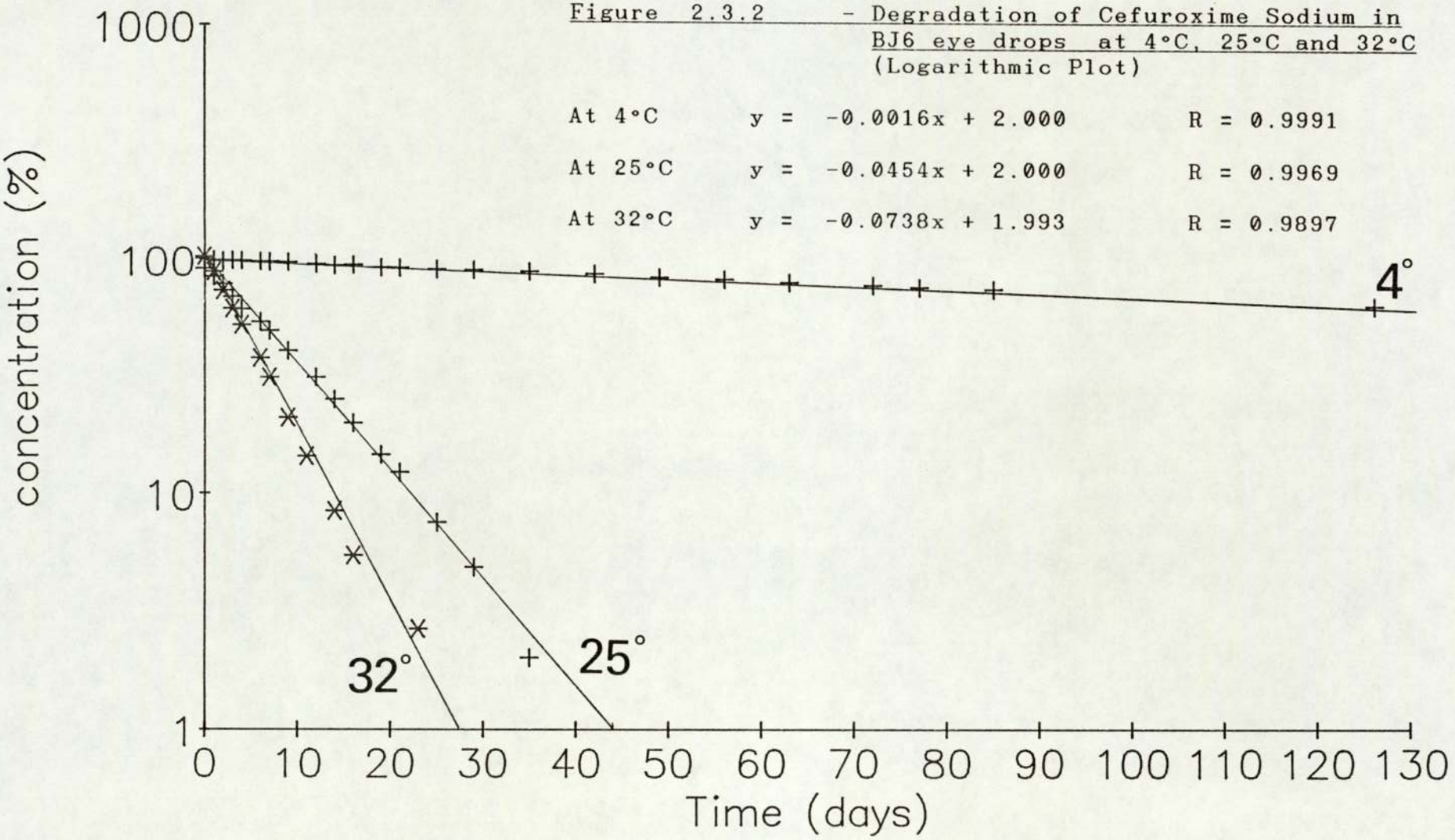


Table 2.3.15 - Stability of Cefuroxime Sodium in Hypromellose Preservative Free Eye Drops

Day	Percentage of Nominal Concentration Remaining 4°C		25°C		32°C	
0	101.55	(1.32)	93.13	(0.69)	102.62	(1.18)
1	99.56	(0.77)	87.09	(0.59)	84.88	(0.52)
2	100.15	(1.28)	78.62	(1.20)	69.57	(2.97)
3	99.02	(0.20)	70.03	(0.75)	59.07	(1.75)
4	98.94	(0.36)	64.50	(0.69)	50.82	(2.02)
6	98.41	(0.67)	55.34	(0.89)	37.55	(2.74)
7	97.24	(0.29)	50.23	(0.59)	28.71	(1.36)
9	97.38	(0.68)	41.38	(0.78)	20.15	(1.58)
11					13.87	(1.39)
12	95.97	(0.94)	31.75	(0.64)		
14	94.11	(0.97)	26.03	(0.29)	8.47	(1.01)
16	93.29	(2.33)	21.56	(0.47)		
19	93.23	(1.18)	15.72	(0.36)		
21	92.76	(1.06)	12.91	(0.52)		
23						
25	91.89	(1.07)	8.80	(0.93)		
29	91.04	(0.45)	5.61	(0.86)		
35	88.44	(0.91)	2.49	(0.07)		
42	86.35	(1.00)				
49	84.21	(0.45)				
56	81.87	(2.29)				
63	79.51	(0.84)				
72	77.81	(0.64)				
77	77.21	(1.23)				
85	75.46	(0.81)				
126	64.99	(0.20)				
127	65.36	(0.11)				

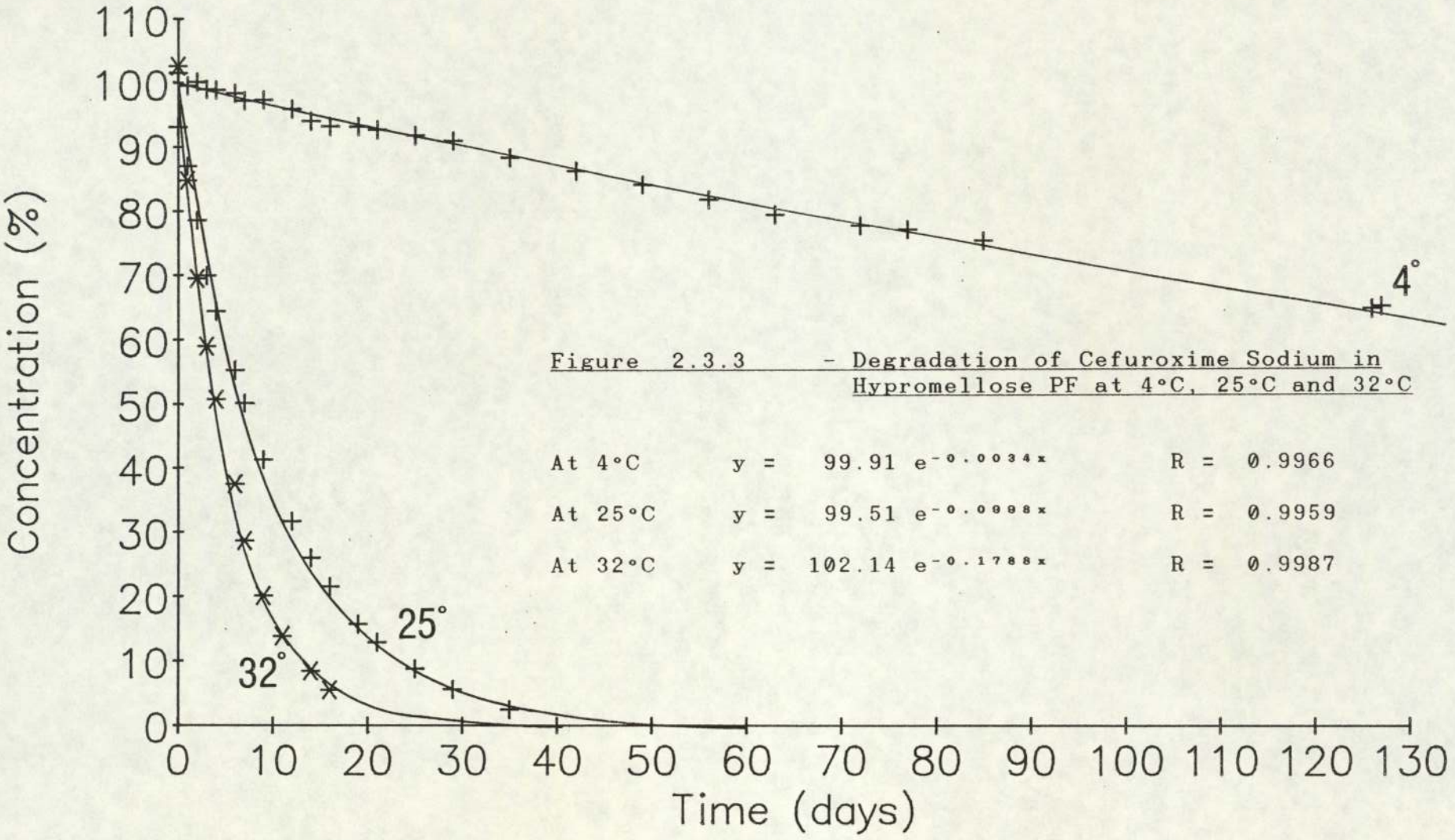


Figure 2.3.3 - Degradation of Cefuroxime Sodium in Hypromellose PF at 4°C, 25°C and 32°C

At 4°C	$y = 99.91\ e^{-0.0034x}$	R = 0.9966
At 25°C	$y = 99.51\ e^{-0.0098x}$	R = 0.9959
At 32°C	$y = 102.14\ e^{-0.1788x}$	R = 0.9987

Figure 2.3.4 - Degradation of Cefuroxime Sodium in Hypromellose PF at 4°C, 25°C and 32°C (Logarithmic Plot)

At 4°C y = -0.0015x + 2.000 R = 0.9977

At 25°C y = -0.0434x + 1.998 R = 0.9979

At 32°C y = -0.0706x + 1.977 R = 0.9962

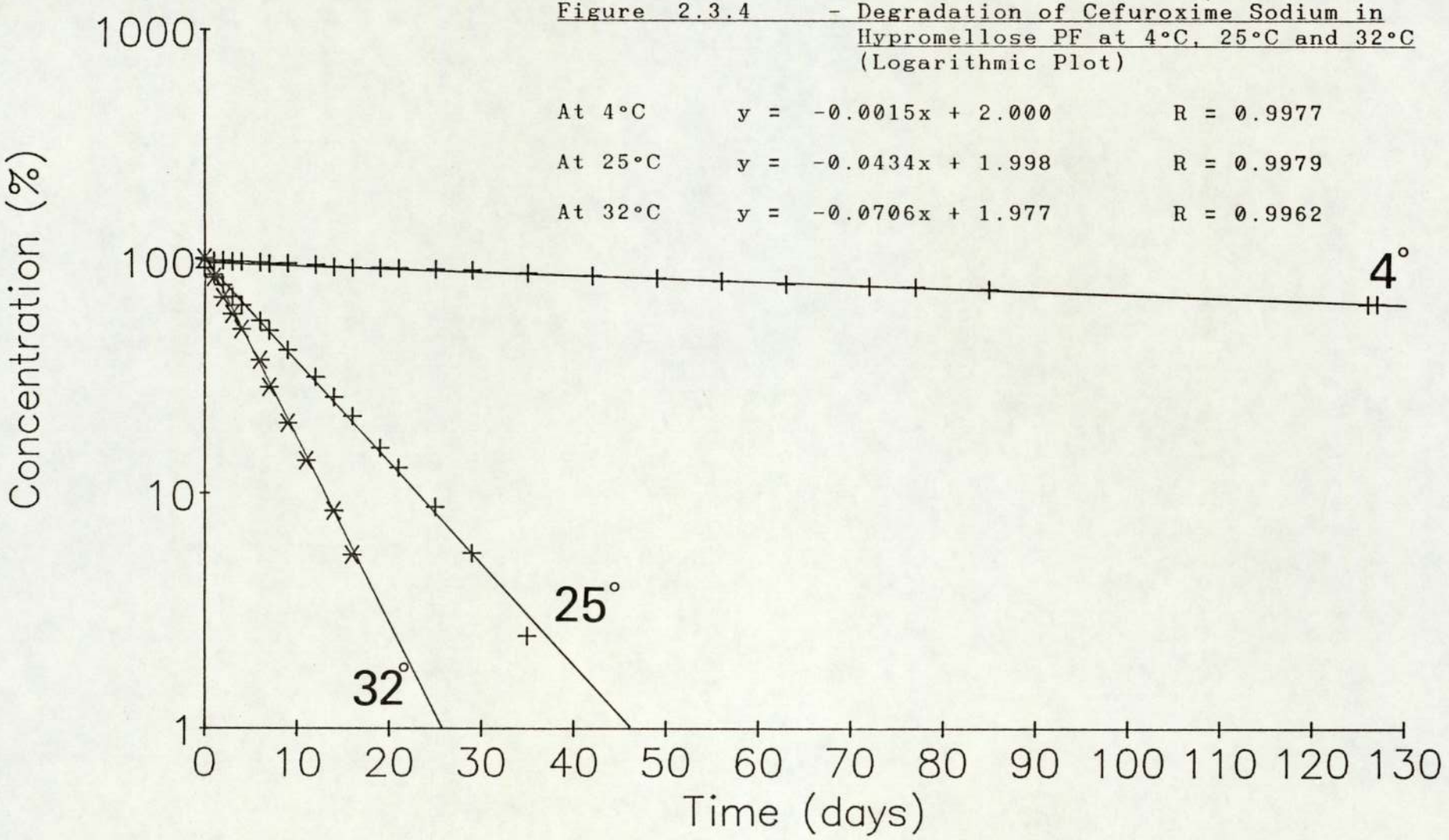


Table 2.3.16 - Stability of Cefuroxime Sodium in Sno Tears

Day	Percentage of Nominal Concentration Remaining 4°C		25°C		32°C	
0	100.25	(2.32)	94.84	(1.66)	95.94	(2.44)
1	99.12	(1.03)	86.46	(1.78)	85.95	(1.40)
2	99.45	(1.11)	81.26	(1.42)	71.50	(1.81)
3	99.73	(0.68)	73.08	(1.62)	61.47	(0.50)
4	99.92	(0.70)	67.05	(2.06)	53.23	(1.12)
6	100.01	(0.61)	60.26	(2.46)	39.50	(0.72)
7	97.91	(0.39)	54.50	(3.74)	31.69	(0.50)
9	97.69	(0.54)	44.53	(2.19)	23.04	(1.53)
11					15.89	(1.40)
12	98.11	(0.57)	36.55	(0.78)		
14	97.02	(0.46)	32.71	(0.79)	9.42	(0.11)
16	95.77	(0.83)	26.19	(0.59)	6.60	(0.29)
19	94.52	(0.32)	21.35	(1.83)		
21	93.12	(0.48)	16.37	(1.22)		
23					1.95	(0.41)
25	93.40	(0.83)	11.40	(0.69)		
29	91.28	(0.40)	7.63	(0.92)		
35	90.81	(0.02)	4.40	(0.54)		
42	90.09	(0.08)	2.37	(0.12)		
49	86.89	(0.13)	1.98	(0.23)		
56	84.77	(0.12)				
63	84.16	(0.49)				
72	81.83	(0.17)				
77	82.17	(0.45)				
85	79.17	(2.46)				
125	73.35	(0.20)				
126	73.28	(0.14)				
152	67.12	(0.23)				

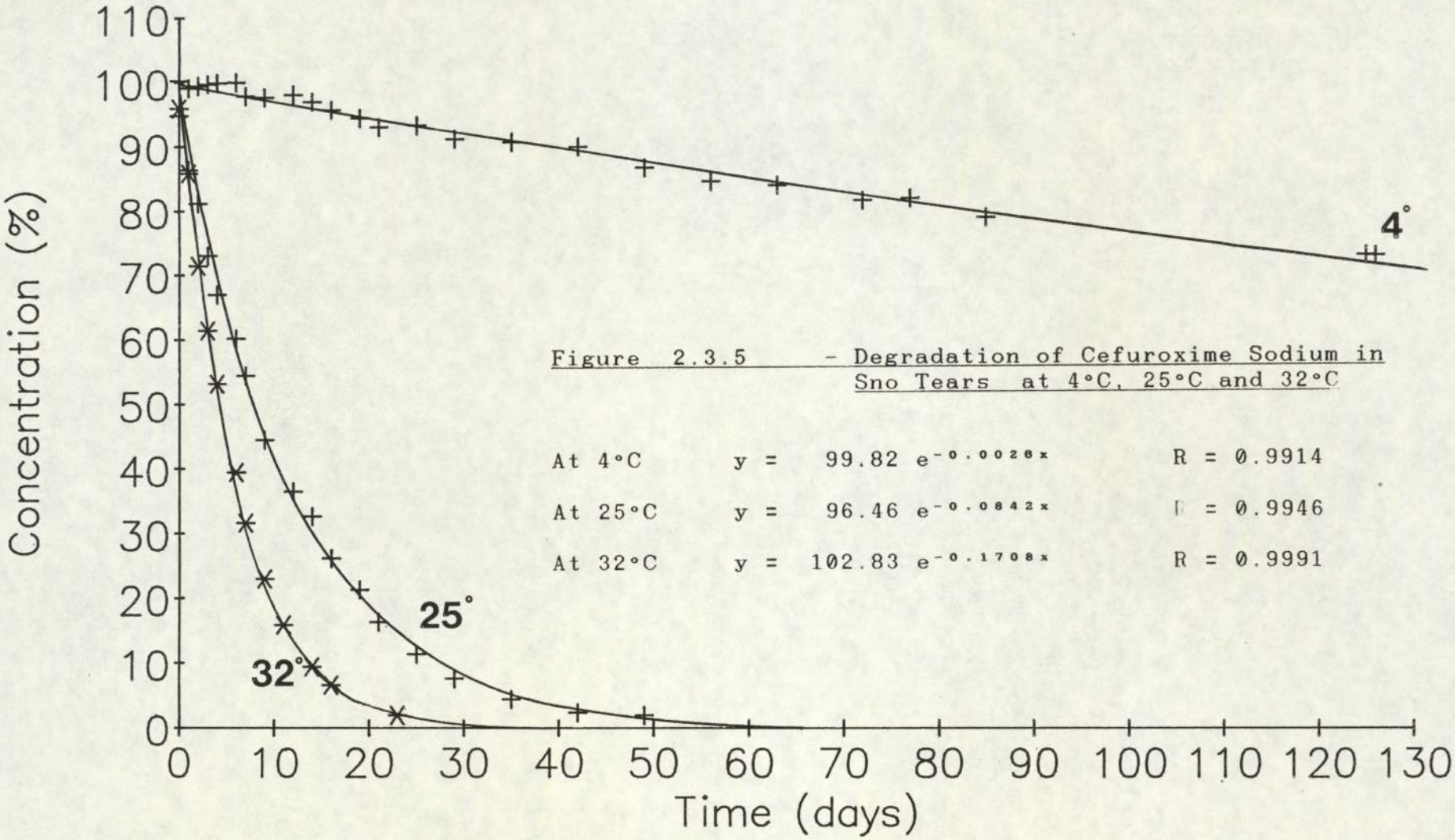


Figure 2.3.5 - Degradation of Cefuroxime Sodium in Sno Tears at 4°C, 25°C and 32°C

At 4°C	$y = 99.82\ e^{-0.0026x}$	R = 0.9914
At 25°C	$y = 96.46\ e^{-0.0842x}$	R = 0.9946
At 32°C	$y = 102.83\ e^{-0.1708x}$	R = 0.9991

Figure 2.3.6 - Degradation of Cefuroxime Sodium in Sno Tears at 4°C, 25°C and 32°C (Logarithmic Plot)

at 4°C y = -0.0011x + 1.999 R = 0.9957

At 25°C y = -0.0365x + 1.984 R = 0.9973

At 32°C y = -0.0703x + 1.993 R = 0.9985

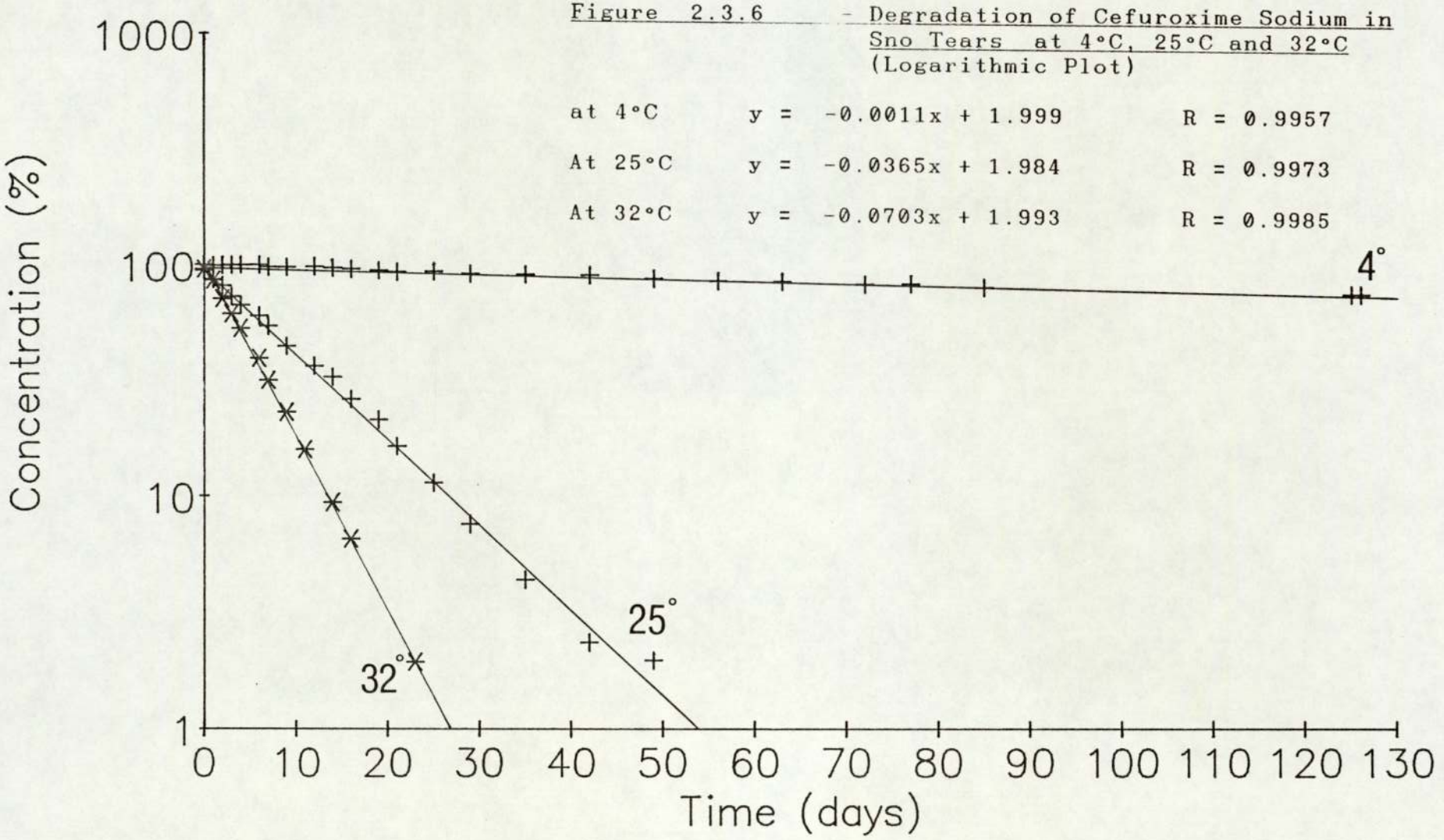


Table 2.3.17 - Stability of Cefuroxime Sodium in Distilled Water

Day	Percentage of Nominal Concentration Remaining 4°C		25°C		32°C	
0	101.26	(1.01)	94.31	(0.56)	91.71	(2.80)
1	100.36	(0.52)	88.14	(2.06)	85.00	(3.66)
2	100.42	(0.69)	83.46	(0.92)	72.17	(2.54)
3	99.49	(0.24)	74.63	(1.39)	61.95	(1.90)
4	98.51	(0.46)	67.45	(1.24)	52.75	(1.41)
6	98.72	(0.39)	60.75	(0.80)	38.94	(1.43)
7	98.11	(0.58)	55.82	(1.11)	31.40	(1.45)
9	97.34	(0.20)	47.14	(1.26)	22.64	(1.10)
11					15.16	(1.07)
12	96.83	(0.49)	36.23	(1.26)		
14	96.66	(0.43)	29.10	(2.61)	8.97	(0.76)
16	96.66	(1.07)	24.15	(0.75)	6.10	(0.52)
19	95.27	(0.23)	18.45	(1.03)		
21	95.35	(0.16)	15.34	(1.39)		
23						
25	94.33	(0.21)	10.67	(0.33)		
29	93.24	(0.54)	7.23	(0.64)		
35	92.07	(0.41)	4.26	(0.58)		
42	90.69	(1.11)				
49	89.92	(0.35)				
56	88.07	(0.84)				
63	86.80	(1.21)				
72	84.65	(0.06)				
77	83.64	(0.32)				
85	80.19	(3.58)				
114	72.86	(0.20)				

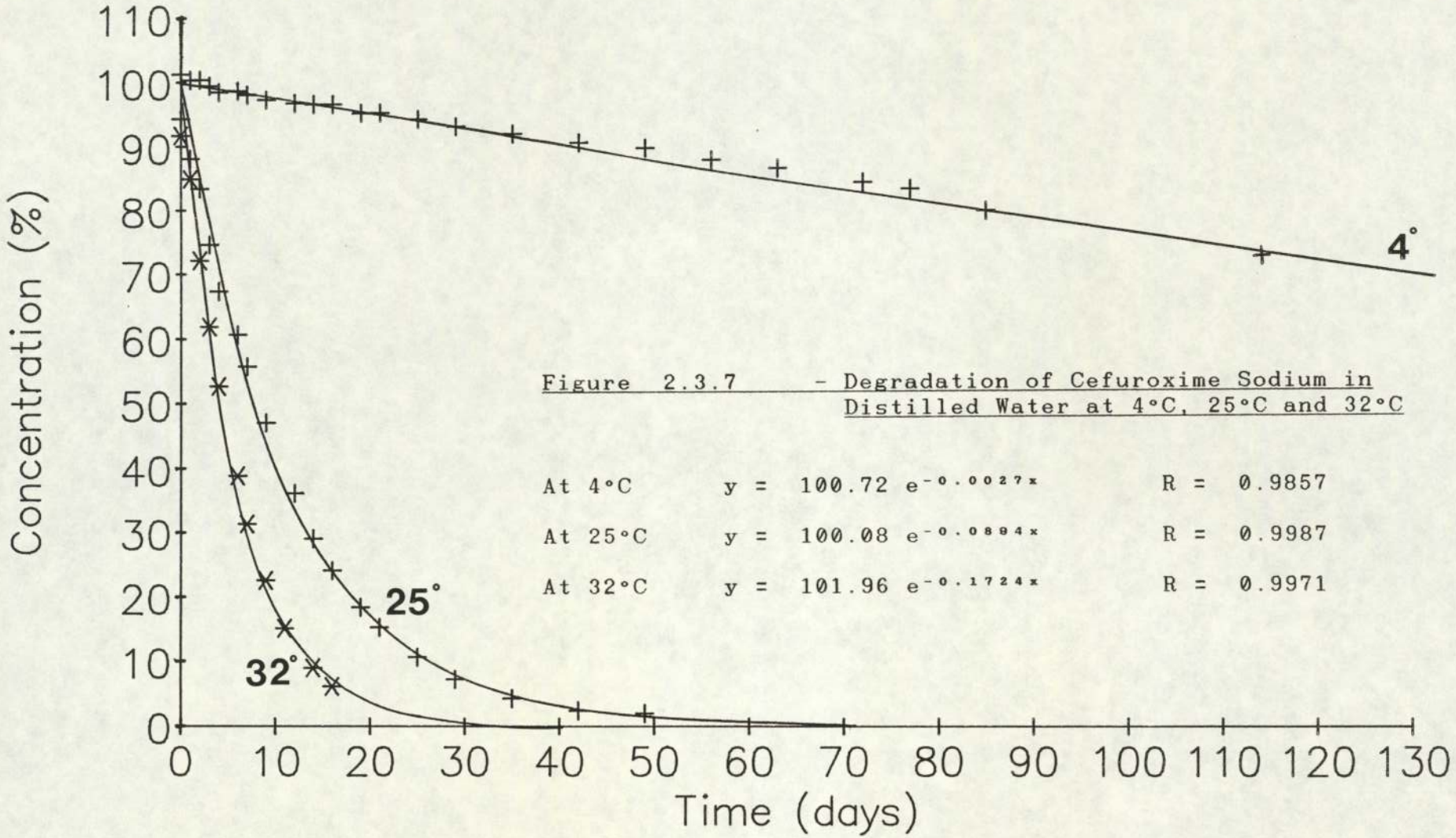


Figure 2.3.7 - Degradation of Cefuroxime Sodium in Distilled Water at 4°C, 25°C and 32°C

At 4°C	$y = 100.72\ e^{-0.0027x}$	R = 0.9857
At 25°C	$y = 100.08\ e^{-0.0894x}$	R = 0.9987
At 32°C	$y = 101.96\ e^{-0.1724x}$	R = 0.9971

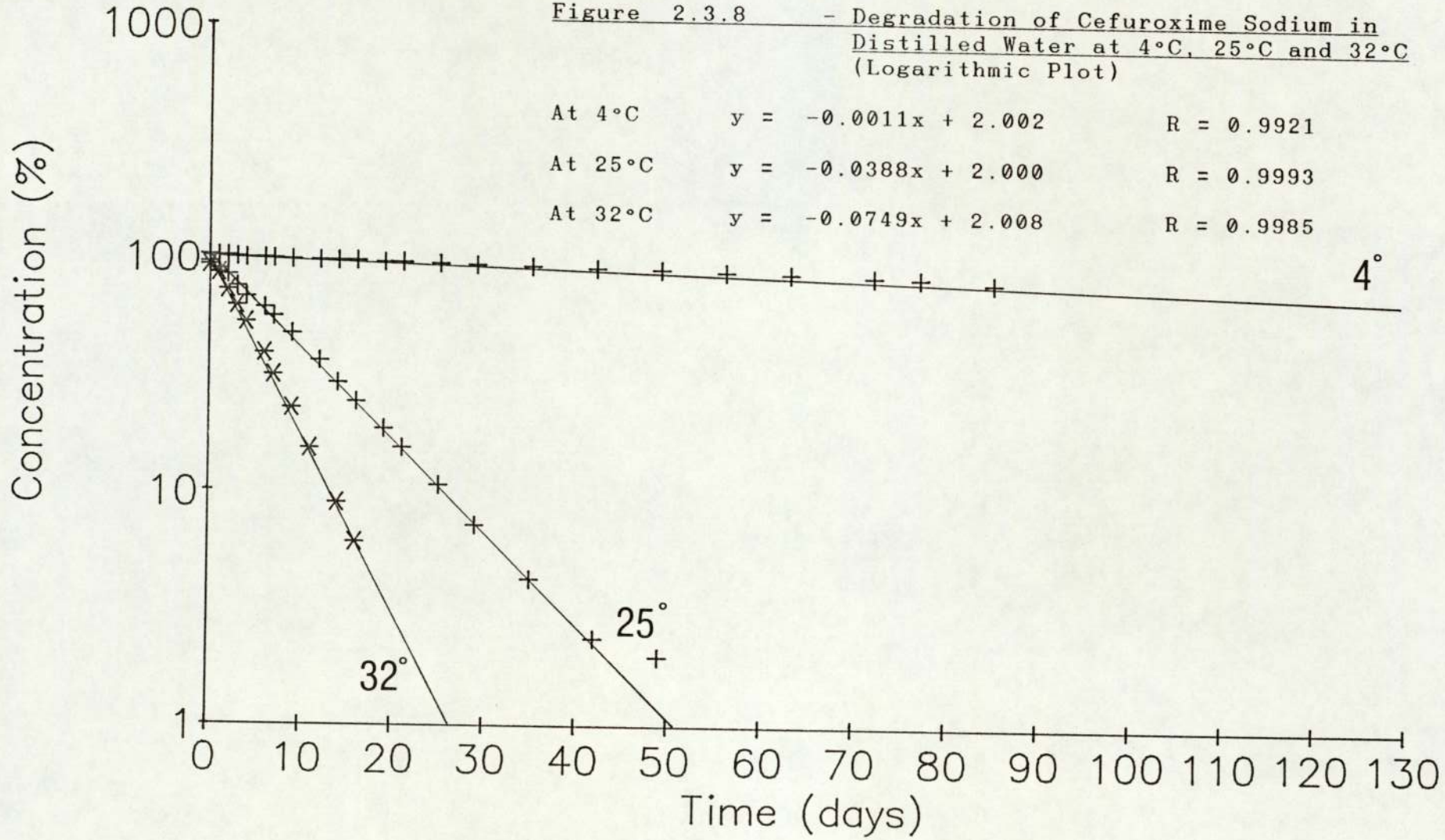


Figure 2.3.8 - Degradation of Cefuroxime Sodium in Distilled Water at 4°C, 25°C and 32°C (Logarithmic Plot)

At 4°C	y = -0.0011x + 2.002	R = 0.9921
At 25°C	y = -0.0388x + 2.000	R = 0.9993
At 32°C	y = -0.0749x + 2.008	R = 0.9985

2.3.6 Preservative Testing

The BP test to confirm preservative efficacy was carried out on the most suitable product identified from the earlier sections. This was the formulation of cefuroxime 50mg/ml in Sno Tears.

Table 2.3.18 - Colony Counts for BP Preservative Test

Time	Numbers of cells per ml ($x10^6$)					
	Candida albicans		Pseudomonas aeruginosa		Staphylococcus aureus	
	test	control	test	control	test	control
0 hours	1.7	1.3	1.8	1.5	1.7	1.4
6 hours	0.0	6.3	0.0	19.2	0.0	32.3
24 hours	0.0	13.7	0.0	663.7	0.0	810.0
7 days	0.0	216.3	0.0	142.0	0.0	1023.0
14 days	0.0	174.0	0.0	133.0	0.0	1480.0
28 days	0.0	62.3	0.0	198.7	0.0	300.0

The control preparations of each organism showed growth throughout the test period, showing that the inoculum was viable in each case. All active test samples showed growth at the time of initial challenge, but showed no growth thereafter.

Therefore the preparation of cefuroxime in Sno tears over a 28 day period complies with the BP test for preservative efficacy.

2.4 DISCUSSION

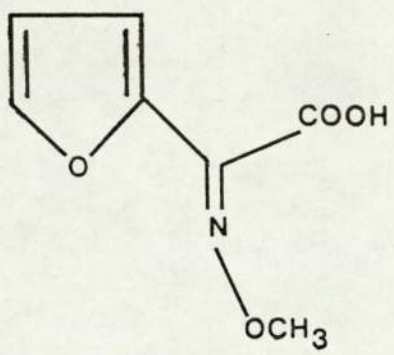
Cefuroxime degradation products elute with relative retention times of 0.31 and 0.79 when compared with the retention time of cefuroxime.

Table 2.4.1 - Relative Retention Times of Degradation Products

Compound	Relative Retention Time
Cefuroxime	1.00
Compound I	0.31
Compound II	0.79

Comparision of these data with that work carried out by Coomber, Jefferies and Woodford suggests that these compounds may be (Z)-2-(2-furyl)-2-methoxyiminoacetic acid (I) and (6R,7R,2Z)-7-[2-(2-furyl)-2-methyoxyiminoacetic - amide]-3-hydroxymethylceph-3-em-4-carboxylic acid (II).

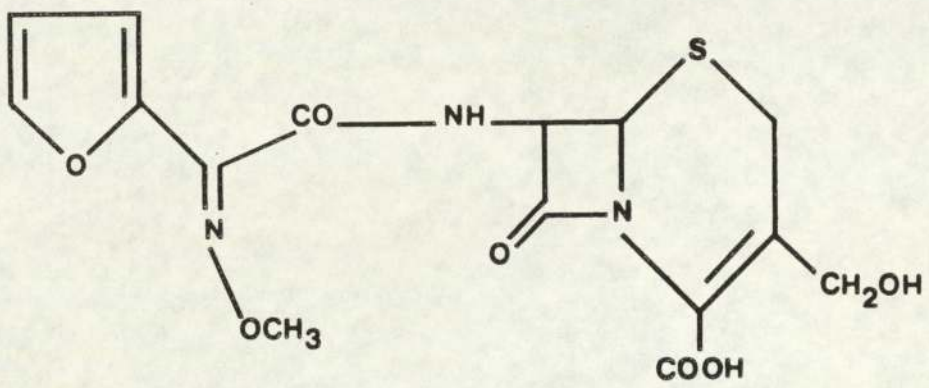
Figure 2.4.1 - Chemical Structure of Compound I



This is supported by a general scheme of decomposition of cephalosporins suggested by Conners, Amidon & Kennon, where

high pH degradation products arise from hydrolysis of the side chain.

Figure 2.4.2 - Chemical Structure of Compound II



The time taken for 10% of the initial concentration to be lost by degradation is often used as an arbitary measure of the shelf life of a pharmaceutical product.

The 10% degradation time can be calculated from the first order degradation rate constant (k), where the concentration is decreasing exponentially with time according to the equation

$$C_t = C_o \, e^{-kt}$$

This equation can be considered in terms of base 10 logarithms to give the equation

$$\log C = \log C_o - (kt / 2.303)$$

Using the first order degradation rate constants obtained, a shelf life can be calculated for each formulation, at 4°C, 25°C and 32°C.

Table 2.4.2 - Shelf Life of Cefuroxime Eye Drop Formulations

Formulation	10% Degradation (days) 4°C	25°C	32°C
BJ6	28.51	1.01	0.63
Hypromellose Pres Free	31.03	1.06	0.59
Sno Tears	40.58	1.25	0.62
Distilled Water	39.07	1.18	0.61

A Student's `t-test' carried out on the k values showed no significant difference between different formulations at each temperature. The observed differences in k are very small.

However when these values are used to calculate a shelf life for each product the difference seen is more important. The calculated shelf life of the formulations in BJ6 and Hypromellose Preservative Free Eye Drops are in the region of 10 days shorter than seen for Sno Tears and Distilled Water. This observation probably reflects the fact that these two products fall within the maximum pH stability range of cefuroxime (pH 4.5 - 7.3), while BJ6 Eye drops and Hypromellose Preservative Free eye drops are both outside this.

Although there is only a difference of 1 day between the calculated shelf life of the Sno Tears formulation and the simple solution in water the Sno Tears formulation is an economically more viable product to use when Cefuroxime eye drops need to be extemporaneously prepared. The presence of a preservative in this formulation means that it does not

need to be replaced every 24 hours as the preservative free Water formulation would need to be.

During the past 2 years 7 patients have been treated at the Birmingham and Midland Eye Hospital with Cefuroxime eye drops, made as a simple solution in water and given a 3 day shelf life as recommended in the Moorfields Pharmacopoeia 1985. Treatment length ranged from 3 days to 16 days, necessitating the extemporaneous manufacture of between 1 and 6 batches of eye drops at 3 day intervals. At least 3 bottles per batch must be prepared to allow for a new bottle to be opened every 24 hours.

The data obtained from the quantitative stability studies of cefuroxime in BJ6, Hypromellose Preservative free Eye drops, Sno Tears and Distilled Water indicate that in all 7 cases the preparation of a single batch of eye drops would have been sufficient to complete treatment, if stored at 4°C, resulting in a considerable saving in manufacturing time.

The stability investigations carried out at 25°C, indicate that at this temperature, all four formulations have a shelf life of approximately one day. As Cefuroxime eye drops are frequently prescribed for use every hour or half hour, at the Birmingham and Midland Eye Hospital they are often kept by the bedside for instillation by the patient. The instillation of "cold" eye drops into the eye is uncomfortable and refrigeration of eye drops used at such frequent intervals is usually considered to be impractical. Therefore it is important that the eye drops are replaced each day, even though the formulations in Sno Tears and BJ6

are not preservative free, the usual reason for 24 hour replacement. In cases where the eye drops are prescribed less frequently there is no reason why they should not be refrigerated on the ward.

A number of factors other than concentration may affect the rate of a reaction. These include temperature, solvents, catalysts and light. The speed of many reactions increases between 2 and 3 times with each 10 degree rise in temperature. The effect of temperature on reaction rate is given by the equation, suggested by Arrhenius;

$$k = Ae^{-E_a/RT}$$

This can be expressed in terms of base 10 logarithms as

$$\log k = \log A - \frac{E_a}{2.303} \times \frac{1}{RT}$$

where R is the gas constant, E_a the energy of activation, A the frequency factor of the reaction and T the absolute temperature. By plotting 1/T against log k a straight line is obtained with an intercept of log A and slope of $-E_a/2.303\ R$.

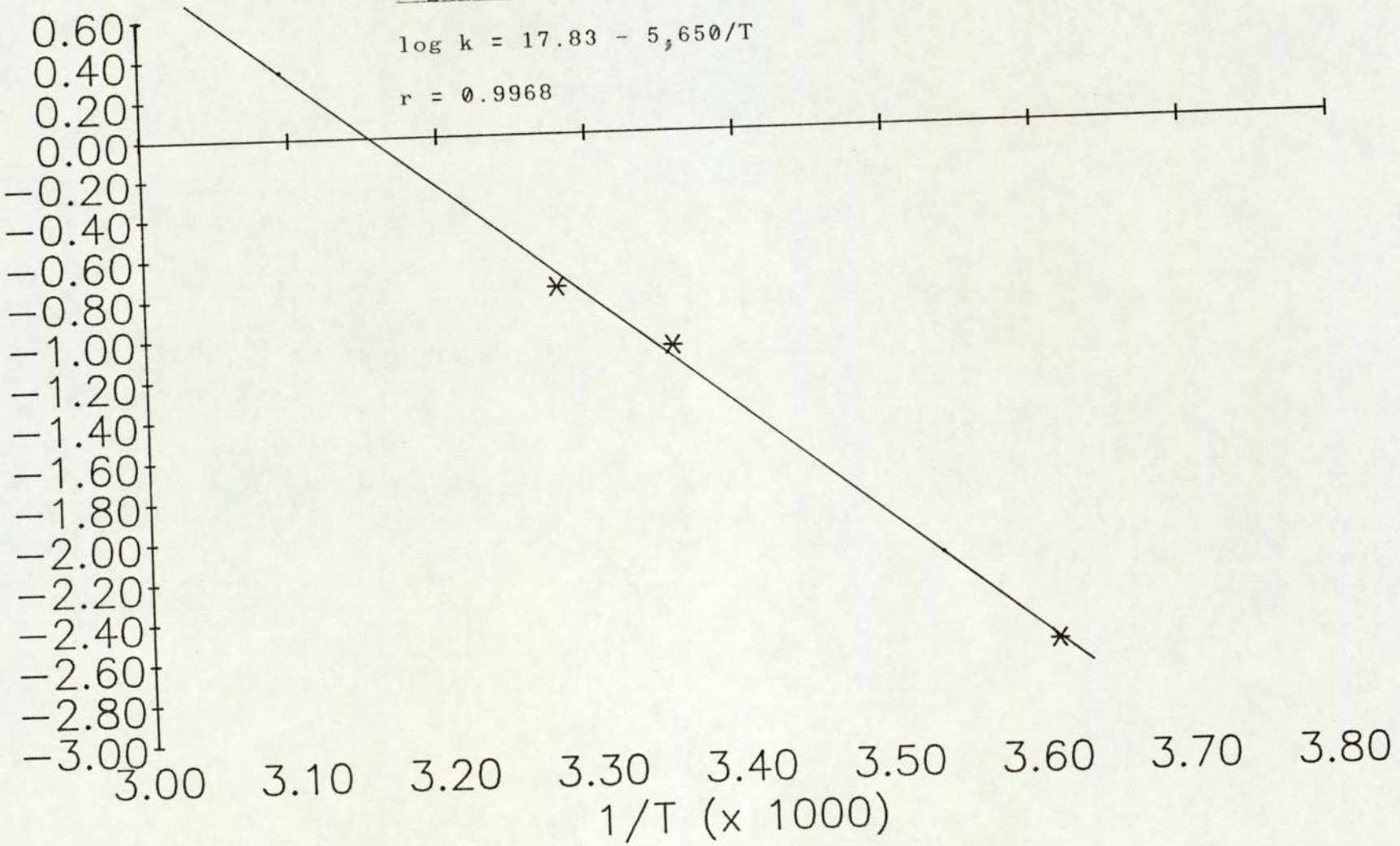
By using an Arrhenius plot of degradation rate constant values at a number of temperatures, the degradation rate of a product can be predicted at temperatures other than those initially investigated.

From Figure 2.4.3 the energy of activation (E_a) for the degradation of Cefuroxime in Sno Tears can be calculated to be 108.1 kJ/mole and the frequency factor (A) of the reaction to be 6.76×10^{17}.

Figure 2.4.3 - Arrhenius Plot of Cefuroxime in Sno Tears

log k = 17.83 - 5,650/T

r = 0.9968



This information can be used to predict the degradation rate constant and therefore shelf life of Cefuroxime eye drops prepared in Sno Tears when stored at various temperatures.

Table 2.4.3 - Shelf Life of Cefuroxime in Sno Tears At Various Temperatures

Temperature °C	Degradation rate constant (k)	Shelf Life (days)
0	0.0014	75.286
10	0.0074	14.243
20	0.0350	3.011
30	0.1514	0.696
40	0.6026	0.175
50	2.1878	0.048
60	7.2444	0.015
70	22.9087	0.005

2.5 CONCLUSIONS

The use of a formulation containing a viscosity agent is considered to be an advantage, due to the increased contact time with the eye and the enhanced drug penetration associated with it. The presence of both a viscosity agent and preservative confer even greater advantage.

The formulation which most closely fits the desired criteria is that of cefuroxime in Sno Tears. This product has a shelf life as long as that seen with the simple solution in water, and longer than the alternatives in Hypromellose Preservative free and BJ6 Eye drops. It contains a preservative allowing for use of more than 24 hours if stored at 4°C, and a viscosity agent to enhance penetration into the eye.

In the situation where a preservative-free formulation is required due to intolerance of the patient to benzalkonium, the choice lies between the simple solution in water and the formulation in Hypromellose Preservative-free Eye drops. Although the shelf life of the Hypromellose Preservative-free product is shorter, it has the advantage of containing a viscosity agent which will enhance penetration, and is probably to be favoured.

PART 3

FINAL CONCLUSIONS

Following the identification of the need for a single publication covering the dosage and preparation of ophthalmic injections a booklet has been prepared which covers this subject. This publication; "Periocular and Intraocular Injections : A Guide for Pharmacists" will shortly be available from the Guild of Hospital Pharmacists.

The identified need for formulation and stability data on the preparation of Cefuroxime eye drops has resulted in the recommendation that these be prepared by the addition of cefuroxime to Sno Tears (Smith & Nephew). When stored at 4°C, either refrigerated in the Pharmaceutical Department following manufacture, or on the ward, these eye drops can safely be considered to have a shelf life in excess of one month. In the situation where they are stored at room temperature, either by accident or on the ward, cefuroxime prepared in Sno Tears should be used within 24 hours.

The response obtained from both questionnaires indicate that information about the practical application of pharmacy in this specialist area of ophthalmology is sparse. Further practice research in the areas of drug information and formulation are needed in this field.

APPENDIX I

PILOT QUESTIONNAIRE

QUESTIONNAIRE RELATING TO INTRAOCULAR INJECTIONS

Please complete and return to the Pharmacy Department, Birmingham and Midland Eye Hospital, Church Street, Birmingham.

1. When issuing subconjunctival, intravitreal and intracameral injections in your hospital, in what form are they issued?

[ ] a) Just the injection vial

[ ] b) Injection vial plus information regarding dilution to an appropriate dose.

[ ] c) Single-dose ready-prepared injection to give straight to the patient

[ ] d) Other - please specify.....

If 1c,

Please give information regarding stability, shelf-life, storage conditions etc, of the product

2. Which of the following preparations do you use in your hospital?
Please indicate the approxiamte usage of each preparation and also the product you prefer to use. Space has been left for you to add any other drugs you may use intra-ocularly.

DRUG		ANNUAL USAGE		
Approved Name	Your preferred product	Subconjunctival	Intracameral	Intravitreal
Ampicillin				
Benzylpenicillin				
Methicillin				
Azlocillin				
Piperacillin				
Ticarcillin				
Carbenicillin				
Mezlocillin				
Cefotaxime				
Cephradine				
Cefsulodin				
Cephazolin				
Cephalothin				
Cephamandole				
Cefuroxime				
Latamoxef				
Kanamycin				
Gentamicin				
Tobramycin				
Amikacin				
Framycetin				
Clindamycin				
Lincomycin				
Vancomycin				
Erythromycin				
Colistin				
Polymixin				
Chloramphenicol				
Amphotericin				
Miconazole				
Nystatin				
Acyclovir				
Methylprednisolone				
Triamcinolone				
Dexamethasone				
Betamethasone				
Any other drugs used				

3. Would you be interested in information about how to prepare introcular injections and the prefered products to use ?

YES [ ] NO [ ]

4. Have you any information about mixing introcular injections and subsequent stability of the mixed injection ?
If so, please specify.....

5. If a national service for the production of intraocular injections was set up, would you be interested in supporting it ?

YES [ ] NO [ ]

APPENDIX II

FINAL QUESTIONNAIRE

QUESTIONNAIRE RELATING TO OPHTHALMIC INJECTIONS

Please complete by ticking the box or writing in the space provided. Return in the envelope provided to Hilary Scott, Pharmacy department, Birmingham and Midland Eye Hospital, Church Street, Birmingham.

Please give as many details as possible as any information at all will be useful. If you have any queries about the completion of this questionnaire please contact me on : 021 - 236 - 4911 extension 224.

Pharmacist in Charge
Pharmacy Department
Hospital Name and Address

1. When issueing subconjunctival, intravitreal and intracameral injections in your hospital, in what form are they issued?

[ ] a) Just the injection vial

[ ] b) Injection vial plus information regarding dilution to an appropriate dose.

[ ] c) Single-dose ready-prepared injection to give straight to the patient

[ ] d) Other - please specify.....

If 1c,

Please give any information you have regarding stability, shelf-life, storage conditions etc, of the product.

2. Which of the following preparations do you use in your hospital ? Please indicate the approximate usage of each preparation and the brand or manufacturer who product you prefer to use.

DRUG		ANNUAL USAGE		
Approved Name	Prefered brand or manufacturer	Sub - conjunctival	Intra- cameral	Intra- vitreal
Ampicillin				
Azlocillin				
Benzylpenicillin				
Carbenicillin				
Methicillin				
Mezlocillin				
Piperacillin				
Ticarcillin				
Cefotaxime				
Cefsulodin				
Ceftazidime				
Cefuroxime				
Cephalothin				
Cephamandole				
Cephazolin				
Cephradine				
Latamoxef				
Amikacin				
Framycetin				
Gentamicin				
Kanamycin				
Tobramycin				
Ciprofloxacin				
Chloramphenicol				
Clindamycin				
Colistin				
Erythromycin				
Lincomycin				
Polymixin				
Vancomycin				
Acyclovir				
Amphotericin				
Miconazole				
Nystatin				
Betamethasone				
Dexamethasone				
Methylprednisolone				
Triamcinolone				
Any other drugs used by these routes				

3. Would you be interested in information about how to prepare ophthalmic injections and the prefered products to use ?

YES [ ] NO [ ]

4. Have you any information about mixing ophthalmic injections and subsequent stability of the mixed injection ?
If so, please specify.....

5. If a national service for the production of ophthalmic injections was set up, would you be interested in supporting it ?

YES [ ] NO [ ]

In case I have any queries about the answers you give, please supply the name and position of the person completing this questionnaire. (Such information will not be passed to any third party).

NAME.....POSITION.....

QUESTIONNAIRE RELATING TO EXTEMPORANEOUSLY PREPARED EYE DROPS

Please complete and return in the envelope provided to Hilary Scott, Pharmacy Department, Birmingham and Midland Eye Hospital, Church Street, Birmingham.

If you have any queries about the completion of this questionnaire please contact me on : 021 - 236 - 4911 extension 224.

Pharmacist in Charge Pharmacy Department Hospital Name and Address

1. Which of the following antibiotic and antifungal preparations do you use in your hospital ?. Please give as many details as possible, as any information at all will be useful.

Only those drugs for which no commercial product is available have been included. Please include any non available strengths of preparations at the end.

DRUG	PHARMACEUTICAL DETAILS					ANNUAL USAGE
Approved Name	Strength	Vehicle/ Formula	Preserv -ative	Shelf Life	Storage	
Ampicillin						
Azlocillin						
Benzylpenicillin						
Carbenicillin						
Methicillin						
Mezlocillin						
Pipercillin						
Ticarcillin						

DRUG	PHARMACEUTICAL DETAILS					ANNUAL USAGE
Approved Name	Strength	Vehicle/ Formula	Preserv -ative	Shelf Life	Storage	
Cefotaxime						
Cefoxitin						
Cefsulodin						
Ceftazidime						
Ceftizoxime						
Cefuroxime						
Cephalothin						
Cephamandole						
Cephazolin						
Cephradine						
Latamoxef						
Amikacin						
Kanamycin						
Ciprofloxacin						
Clindamycin						
Colistin						
Erythromycin						
Lincomycin						
Vancomycin						
Amphotericin						
Miconazole						
Nystatin						
Any other drugs used topically						

2. Have you any information about the stability of the prepared eye drops on which the shelf life is based ?
If so, please specify.....

In case I have any queries about the answers you give, please supply the name and position of the person completing this questionnaire. (Such information will not be passed to any third party).

NAME.....POSITION.....

APPRENDIX III

BOOKLET

PERIOCULAR AND INTRAOCULAR INJECTIONS :

A GUIDE FOR PHARMACISTS

PERIOCULAR AND INTRAOCULAR INJECTIONS

A GUIDE FOR PHARMACISTS

By Miss Hilary F. Scott BSc MRPharmS
Research Pharmacist

Birmingham & Midland Eye Hospital
Church Street
Birmingham

021 - 236 - 4911 Ext 224

AUTHOR'S PREFACE

The Pharmacy Department at the Birmingham and Midland Eye Hospital receives many requests for information about the preparation of periocular and intraocular injections, from surgical and nursing staff and also pharmacists at other hospitals. The increasing demand for information of this nature has led to the production of this booklet.

This small volume is intended to provide dosage recommendations, information about appropriate diluents and products to use, and clear directions for reconstitution and dilution to provide a final solution at a concentration suitable for administration by the routes.

H.S.

Acknowledgements

I am indebted to the Guild of Hospital Pharmacists and Merck, Sharp and Dohme Ltd for making the publication of this booklet possible and to Mrs. L. Titcomb for her assistance in its compilation. Thanks must also go to Mr. R. Pate, Dr. B. Hebron, Mr G. Kirkby, Mr D. Burdett and the staff at the Birmingham and Midland Eye Hospital for their help.

CONTENTS

INTRODUCTION

INTRAOCULAR AND PERIOCULAR INJECTIONS

Penetration of drugs into the eye following topical and systemic administration depends on their lipophilicity. For a drug to penetrate the eye following topical administration, it must pass though a "fat-water-fat sandwich" and so must have the ability to exist in solution as an equilibrium between ionised and non-ionised forms. Following systemic administration, a drug has to cross the "blood-retinal barrier", similar in nature to the "blood-brain barrier". Therefore, for certain drugs, neither topical nor systemic administration leads to appropriate levels intraocularly. Relatively small concentrations of hydrophilic drugs such as penicillins, cephalosporins and aminoglycosides will be found in the aqueous and vitreous humours following even high doses. In contrast, lipophilic drugs such as chloramphenicol and some tetracyclines, will readily cross the "blood-retinal barrier". (1)

For example, the generally poor response of serious ocular infections to systemic or topical treatment is due to poor penetration of the antibiotic into the affected tissues. Although topical administration results in high concentrations of drug in the anterior structures, such as the conjunctiva and cornea, much lower concentrations are achieved in the anterior chamber and minimal concentrations in the posterior ocular structures, the vitreous humour, retina and choroid. (2)

It is however necessary to note that in the inflamed eye the integrity of the blood - ocular barriers is likely to be decreased. The presence of ocular inflammation may result in decreased ocular tissue levels following periocular and intraocular administration due to increased losses to the systemic circulation, but may improve the penetration of parenteral treatment. (1)

PERIOCULAR INJECTIONS

1. SUBCONJUNCTIVAL INJECTION (Figure 2)

Higher concentrations of antibiotic can be obtained in ocular tissues by periocular injection than by a much larger dose given systemically. (3-7) The highest concentration of drug is present in the aqueous and anterior structures such as the cornea and conjunctiva, making it most suitable for the treatment of corneal infections. (8) In some cases detectable levels of drug can be achieved in the vitreous. Subconjunctival injection is the injection of a drug beneath the conjunctiva to form bleb.

Method of Penetration

The fluid spreads by dissecting under the conjunctiva and it is thought that intraocular penetration occurs by two possible routes: by leakage from the bleb through the needle track into the tear film with transcorneal absorption; and by a process of direct penetration. From the bleb the drug may penetrate through and into the sclera then into the aqueous humour by a number of routes: sideways into the cornea and across the corneal endothelium, across the trabecular meshwork, through the iris across the anterior surface, or into the cilary body. Following such an injection minimal concentrations are found in the vitreous and the highest concentration is close to the site of injection. (9)

Method of Administration

The injection is made into the subconjunctival space between Tenon's capsule and the conjunctiva and can be performed in any quadrant. The superotemporal quadrant is theoretically preferable as it is the only quadrant where rectus muscle is not crossed by oblique muscle or tendon, but in practice this region is difficult to access and the inferotemporal quadrant is more convenient. The eye is anaesthetised with a topical local anaesthetic, then the patient is instructed to look up and the lower eyelid is retracted. The conjunctiva is grasped with forceps between the inferior and lateral rectus muscles and midway between the limbus and equator of the eye and the injection is made with a gauge 25 - 27 needle. Following the withdrawal of the needle the puncture is grasped for a short time with the forceps to prevent leakage. (10)

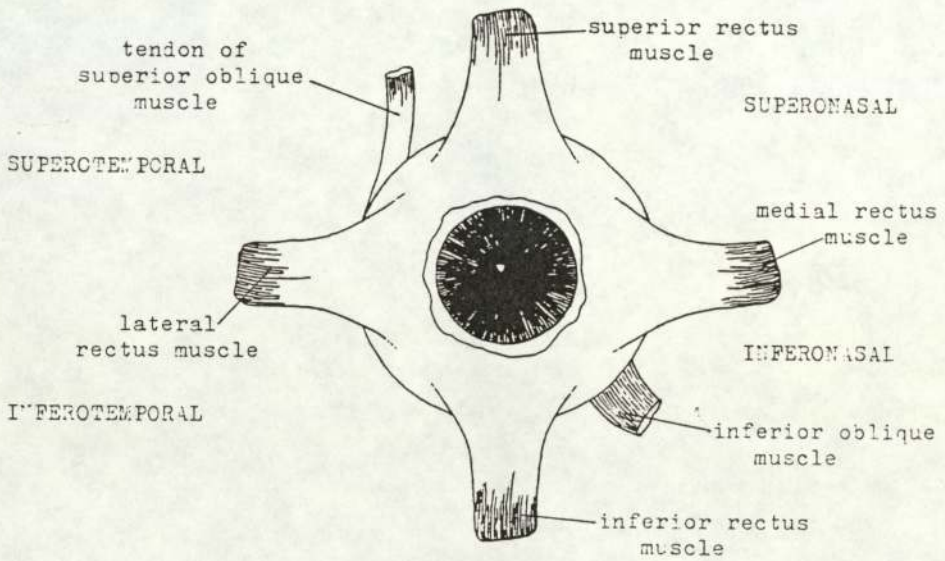


Figure 1 - Position of extraocular muscles (Right eye viewed from the front)

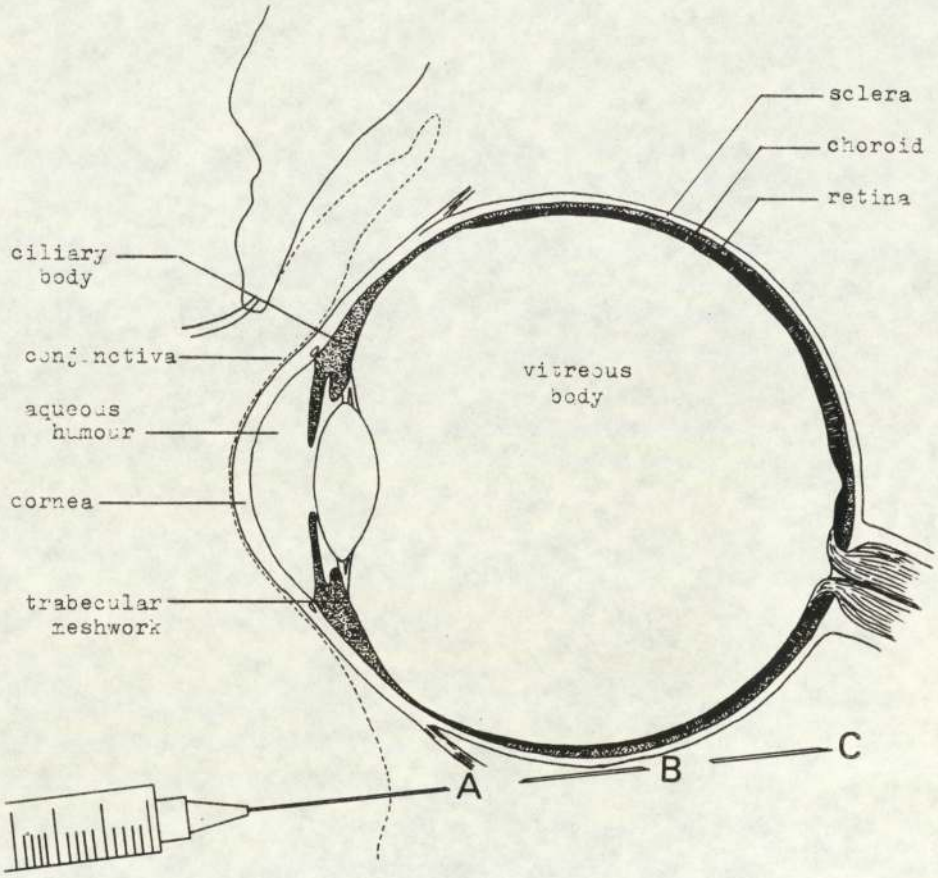


Figure 2 - Relative positions of periocular injections
A - Subconjunctival, B - Anterior Sub - Tenon's,
C - Posterior Sub - Tenon's

2. ANTERIOR SUB - TENON'S INJECTION (Figure 2)
There is very little difference between an anterior sub - Tenon's injection and a subconjunctival injection, and the terms are frequently interchanged. The site of injection is slightly different (See Figure 2) and a lower quantity of drug appears to be delivered to the eye.

Method of Adminstration
After instillation of a topical anaesthetic the patient is instructed to look away. The bulbar conjunctiva and Tenon's capsule are grasped with forceps and a 15mm, 25 gauge needle attached to a tuberculin syringe is passed under the forceps in the desired quadrant. The injection is directed posteriorly in a plane that is parallel to the optic nerve. After attempting blood aspiration the drug is injected slowly into the space beneath Tenon's capsule. (10)

3. POSTERIOR SUB - TENON'S INJECTION (Figure 2)
This type of periocular injection is commonly used for corticosteroids in the treatment of posterior and intermediate uveitis.

Method of Administration
Posterior sub - Tenon's injection is carried out in the same way as the anterior injection. To minimise the risk of perforation of the globe the tip of the needle must

be positioned carefully as it is passed posteriorly to follow the curvature of the globe. The site of injection is similar to that achieved with a retrobulbar injection, and is often preferred as it is usually more comfortable than a retrobulbar procedure. (10)

4. RETROBULBAR INJECTION (Figure 3)

Retrobulbar injection was originally developed to induce anaesthesia of the globe, and this is still its principal use. However antibiotics, corticosteroids and alcohol are also give by this route. Retrobulbar corticosteroids are frequently used in the treatment of posterior inflammatory diseases. The injection is made into the area around the ciliary ganglion, within the muscle cone surrounding the orbit.

Method of Administration

Injection is made through the skin of the lower lid, (as shown in Figure 3), with a 35mm, 25 gauge needle inserted immediately behind the orbital rim and directed towards the apex. It may also be administered through the conjunctiva directly by moving the lower eyelid. The patient is instructed to look up and away from the site of injection to remove the underlying muscles from the injection path. A 50mm needle may be used to produce deeper anaesthesia when complete motor block is necessary. Blood aspiration should be attempted before injection to ensure that a blood vessel has not been punctured. (10)

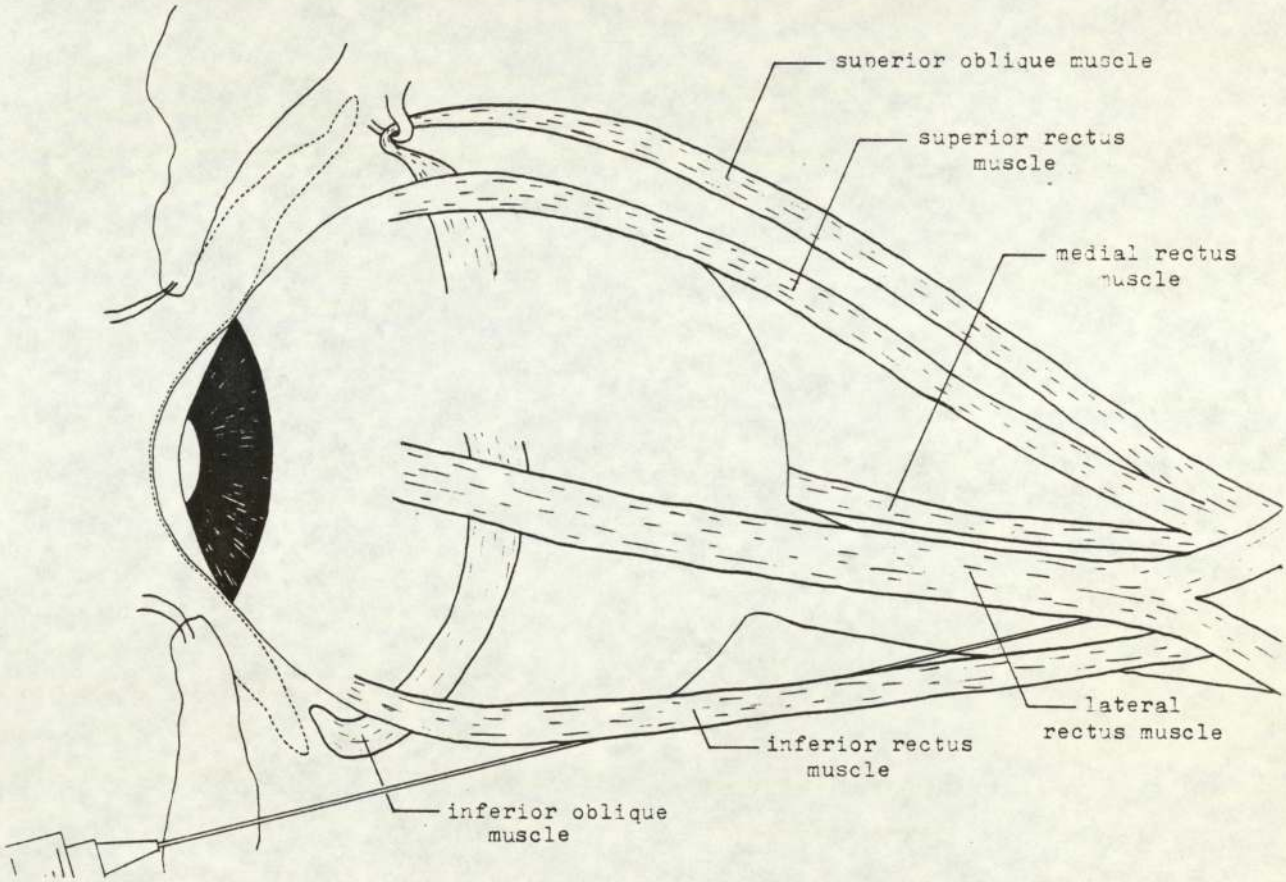


Figure 3 - Position of retrobulbar injection

CONSIDERATIONS IN PERIOCULAR INJECTION PREPARATION

It is not always possible to comply with all the criteria for preparing this type of injection, but the following should be adhered to whenever possible.

i) the solution should be sterile and isotonic.
ii) the solution should be free from excipients such as preservatives. However lignocaine and adrenaline can be used as diluent to decrease pain at the injection site and decrease systemic absorption.
iii) the solution should not be at extremes of pH as this can cause tissue damage.
iv) a) the volume of injection injected by subconjunctival and sub - Tenon's injection should not exceed 0.5ml at one site.
If the dosage required exceeds this volume, injection at more than one site can be made. (NB. in practice some ophthalmologists do inject larger volumes).
b) The volume of injection given by retrobular injection is usually between 1.5 and 6.0ml for anaesthetic solutions and 0.5 to 1ml for other drugs. (10,11)

There is some disagreement whether these injections should be prepared as suspensions or only as solutions. A suspension may require the use of a larger bore needle to allow injection, but may result in a longer acting injection. (Where the method of preparation results in a viscous suspension instructions have also been included for the preparation of a solution).

COMPLICATIONS OF PERIOCULAR INJECTIONS

As this type of injection carries a number of disadvantages it is best reserved for use in the emergency treatment of conditions such as uveitis, or for cases where more conventional treatment has failed. Glaucoma has resulted from the retrobulbar use of corticosteroids and the only method of withdrawing the drug is by surgical removal of the drug deposit.

Complications

Retrobulbar	Subconjunctival & Sub - Tenon's
Accidental perforation of the globe	Transient reduction in visual acuity
Conjunctival and eyelid ecchymosis	Accidental perforation of the globe
Extraocular muscle palsies	Conjunctival and eyelid ecchymosis
Pupillary abnormalities	Subconjunctival haemorrhage
Retrobulbar haemorrhage	Retained deposits
Exposure keratopathy	Dellen formation
CNS or CNS toxicity	Eyelid swelling
Eyelid swelling	Irritated eyes
Optic atrophy	Chemosis
Elevated IOP	Ptosis
Proptosis	Pain
Ptosis	
Pain	

INTRAOCULAR INJECTIONS

As it remains difficult to obtain high drug levels in the vitreoushumour following periocular injection, (12-14) intraocular injection is necessary for drugdelivery to this area.(15-17)THE ADMINISTRATION OF A SOLUTION OF INCORRECT STRENGTH CAN HAVE DISASTROUS CONSEQUENCES AND MAY RESULT IN LOSS OF VISION. (18)

1. INTRAVITREAL INJECTION (Figure 4)

The intravitreal penetration of antibiotics is relatively low following topical, systemic or subconjunctival administration. (1,19-21) As the prognosis of intraocular infection (endophthalmitis) is poor if treated by these routes, direct injection of antibiotics into the vitreous is used. Intravitreal injection may be carried out with or without a vitrectomy being performed.

Method of Administration

This procedure is carried out in the operating theatre as strict aseptic conditions are required. Injection is performed under a general anaesthetic, or with retrobulbar block and topical anaesthesia of the eye.The sclera is exposed in the inferotemporal quadrant approximately 4 - 5mm posterior to the limbus and vitreous is aspirated. It is important to obtain a specimen of vitreous for bacteriological investigation. Vitreous aspiration is carried using a suction cutting device inserted via a routine 20 gauge sclerostomy, under the control of the surgeon. Suction is disconnected and replace by a tuberculin syringe attached to a cannula, via which the assistant gently aspirates the vitreous being cut by the surgeon. The handpiece is withdrawn and the sample sent for investigation. This port can then be utilised for the administration of intravitreal drugs. In the absence of facilities to perform a vitrectomy, small volumes of intravitreal injection, less than 0.2ml, can be administered without vitrectomy.

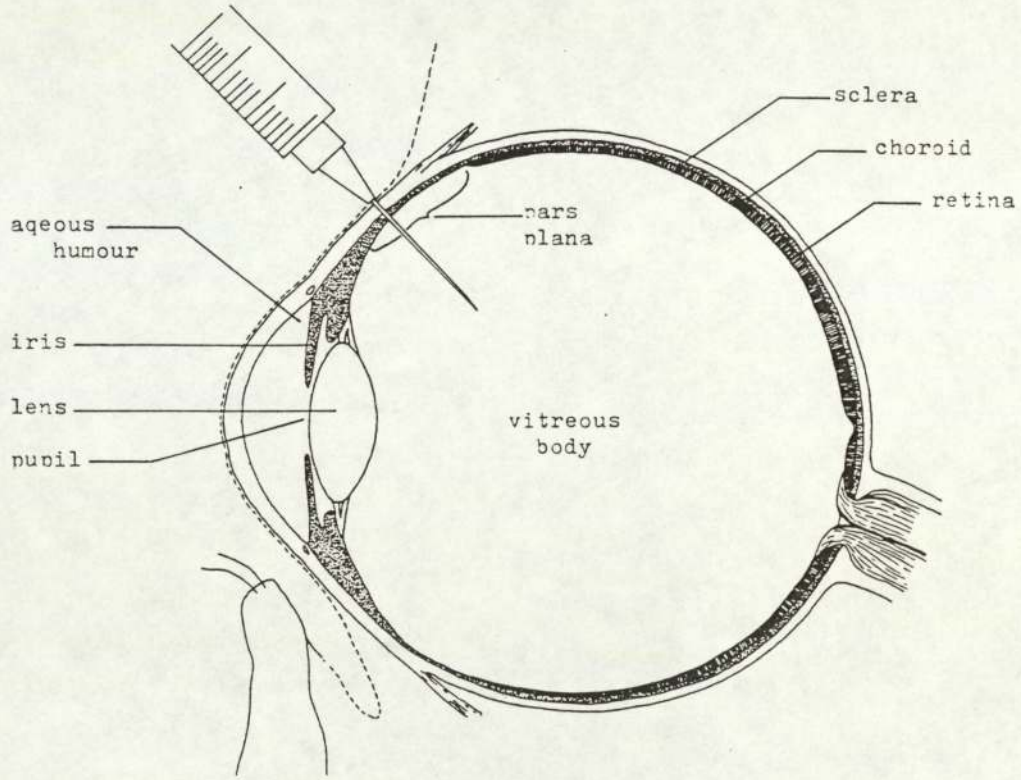


Figure 4 - position of intravitreal injection

Following injection the drug diffuses throughout the vitreous humour and is eventually lost by diffusion into the aqueous humour of the posterior chamber. Some drugs are also lost across the retina, and these drugs, such as the penicillins have a shorter half-life than those which are lost only into the aqueous humour, such as the aminoglycosides. (9) As the cause of endophthalmitis is rarely known, (unless vitrectomy is performed), combinations of antibiotics may be used, often with the addition of a corticosteroid to decrease the inflammation present and lower the risk of secondary damage to the eye. (22)

2. INTRAVITREAL INFUSION

Recently therapeutic vitrectomy has been introduced as a therapy for endophthalmitis. The vitreous is removed, along with the infecting agent and inflammatory cells. During the vitrectomy an antimicrobial containing solution is used to irrigate the area and may be left in the eye as a replacement for the vitreous. (23-26) Although the volume of injection becomes less relevant if a vitrectomy is performed the final concentration of the drug and its toxicity to the retina is important. (27-29) Although this procedure appears to be used in the United States, it is not widely accepted in this country. It is felt to be less safe that intravitreal injection, as it is impossible to know exactly what dosage has been administered.

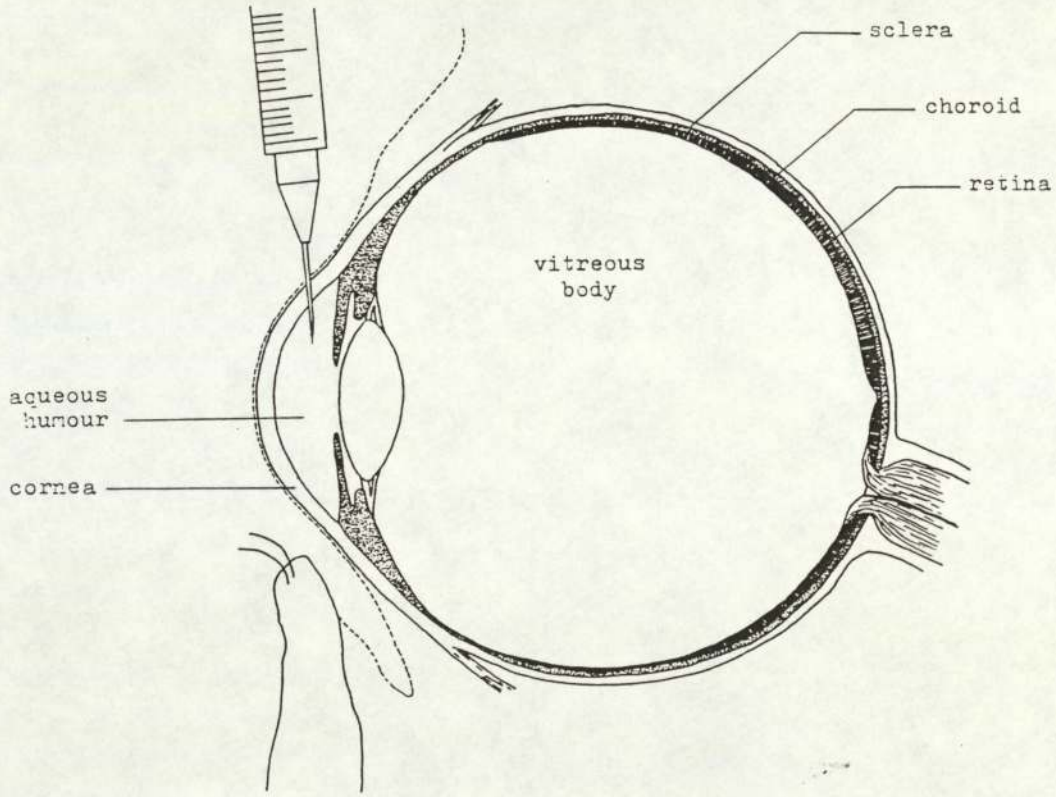


Figure 5 - position of intracameral injection

3. INTRACAMERAL INJECTION (Figure 5)

Intracameral injection involves the injection of drug directly into the anterior chamber of the eye. As high concentrations can usually be obtained in the aqueous humour following subconjunctival and topical treatment, the use of intracameral injection is relatively rare. It may however be considered in the treatment of non sterile conditions requiring surgery such as closure of a penetration wound, or repair of a ruptured operative wound. (10,30)

Method of Administration

This is also an operative procedure requiring strict aseptic conditions, and is usually carriedout under a general anaesthetic, or with retrobulbar and topical anaesthesia of the eye. To prevent an unacceptable increase in the intraocular pressure, aspiration of aqueous humour must be carried out prior to injection, which is made directly into the anterior chamber with a 22 gauge needle. Injection is made peripherally from the side at a shallow angle to prevent penetration of intraocular structures.

CONSIDERATIONS IN INTRAOCULAR INJECTION PREPARATION

It is not always possible to comply with all the criteria for preparing this type of injection, but the following should be adhered to whenever possible.

i) the solution should be sterile and isotonic.
ii) the solution should be free from excipients such as preservatives.
iii) the pH of the solution is not as important if intravitreal injection without vitrectomy is carried out as the volume is highly diluted on administration. The final pH of an intravitreal infusion is more important than the pH of the initial injection used to prepare it.
iv) a) the volume of solution injected by intracameral and intravitreal injection without vitrectomy should not exceed 0.1ml
v) b) the volume of injection given by intravitreal infusion is determined by the volume of the vitreous. More important is the concentration of drug in the solution used.

COMPLICATIONS OF INTRAOCULAR INJECTIONS

Only very minute amounts of drug can be tolerated by the anterior and posterior chambers. EXCESSIVE CONCENTRATIONS CAN RESULT IN SERIOUS DAMAGE TO OCULAR TISSUES.

Complications

Intracameral	Intravitreal
Destruction of corneal endothelium	Invasive intraocular procedure
Dense corneal opacification	Retinal toxicity
Neovascularisation	
Cataract	
Iritis	

NOTES

Where the manufacturer of the preparation recognises this route of adminstration this is indicated in the tables. The use of other drugs by these routes is the responsibility of the individual doctor concerned.

Where no commercial product is available it may be possible to obtain the raw materials necessary to prepare extemporaneously the required formulation. Consult your pharmacy department for further information.

Where products are noted to contain excipients no detailed information is included as formulations may change from time to time. Such information should be obtained from the manufacturers concerned.

Where a brand of drug is mentioned by name this is the only or most suitable product available for the preparation of these injections.

Subconjunctival injection requiring a volume greater than 0.5ml should be administered at two sites.

ABBREVIATIONS

WFI - Water for Injections B.P.

Whilst every effort has been made to ensure the accuracy of the information in this booklet, no responsibility can be accepted for the consequences of any inaccuracies.

DRUG : Acyclovir

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	25mg	Zovirax IV	Add 5ml WFI to 250mg vial to give 250mg in 5ml Administer 25mg in 0.5ml	13, 31 32
intravitreal injection	80 microg	Zovirax IV	Add 10ml WFI to 250mg vial to give 250mg in 10ml Dilute 0.32ml to 10ml with WFI to give 0.8mg in 1ml Administer 80 micrograms in 0.1ml	9, 32 33
intravitreal infusion	20 microg /ml	Zovirax IV	Add 10ml WFI to 250mg vial to give 250mg in 10ml Dilute 0.4ml to 500ml with vitrectomy infusion fluid to give 20 micrograms/ml	9,32
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : The use of acyclovir by subconjunctival injection may be irritant due to the injection being pH 11. Use by this route has been mainly in experimental animals For vitrectomy infusion fluid use Balanced Salt Solution isotonic with ocular tissues, Hartmann's Solution or Ringers Solution

DRUG : Amikacin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	25 - 100mg	Amikin	Commercially available injection containing 250mg/ml Administer 25mg in 0.1ml to 100mg in 0.4ml	9, 34 - 37
intravitreal injection	0.2 - 0.4mg	Amikin	For 0.2mg dilute 0.08ml commercial injection to 10ml with normal saline to give 2mg in 1ml For 0.4mg dilute 0.16ml commercial injection to 10ml with normal saline to give 4mg in 1ml Administer 0.1ml	9, 35 38 - 41
intravitreal infusion	10 microg /ml	Amikin Paediatric	Commercially available injection containing 50mg/ml Dilute 0.1ml to 500ml with vitrectomy infusion fluid to give 10 micrograms/ml	9, 37 38
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : For vitrectomy infusion fluid use Balanced Salt Solution isotonic with ocular tissues, Hartmann's Solution or Ringers Solution.

DRUG : Amoxycillin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	125mg	Amoxil	Add 0.8ml WFI to 250mg vial to give 250mg in 1ml Administer 125mg in 0.5ml	11, 42
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : On reconstitution the solution may be pale pink in colour

DRUG : Amphotericin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	150 - 300 microg	Fungizone	Add 10ml WFI to 50mg vial to give 50mg in 10ml Dilute 1ml to 5ml with WFI to give 1mg in 1ml Administer 150 micrograms in 0.15ml to 300 micrograms in 0.3ml	9, 30 36, 43 - 54
intravitreal injection	5 - 10 microg	Fungizone	Add 10ml WFI to 50mg vial to give 50mg in 10ml For 5 micrograms dilute 0.1ml to 10ml with WFI to give 50 micrograms in 1ml For 10 micrograms dilute 0.1ml to 5ml with WFI to give 100 micrograms in 1ml Administer 0.1ml	9, 10 30, 36 38, 43 48, 52 55 - 66
intravitreal infusion	10 microg /ml	Fungizone	Add 10ml WFI to 50mg vial to give 50mg in 10ml Dilute 1ml to 500ml with vitrectomy infusion fluid to give 10 micrograms/ml	37, 67
intracameral injection	5 - 10 microg	Fungizone	Add 10ml WFI to 50mg vial to give 5mg in 1ml For 5 micrograms dilute 0.1ml to 10ml with WFI to give 50 micrograms in 1ml For 10 micrograms dilute 0.1ml to 5ml with WFI to give 100 micrograms in 1ml Administer 0.1ml	48, 50 65, 68
retrobulbar injection			No information	

COMMENTS : Fungizone contains excipients. On reconstitution the solution is effervescent and needs to stand before use. Subconjunctival injection is painful. For vitrectomy infusion fluid use Balanced Salt Solution isotonic with ocular tissues, Hartmann's Solution or Ringers Solution

DRUG : Ampicillin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	125 - 250mg	Penbritin	Add 0.8ml WFI to 250mg vial to give 250mg in 1ml Administer 125mg in 0.5ml to 250mg in 1ml	9, 11 21, 30 36, 69 - 73
intravitreal injection	5mg	Penbritin	Add 9.6ml WFI to 500mg vial to give 500mg in 10ml Administer 5mg in 0.1ml	9, 10 36, 38 62, 72
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Administer volumes over 0.5ml by subconjunctival injection at two sites.

DRUG : Azlocillin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	100mg	Securopen	Add 1.63ml WFI to 500mg vial to give 500mg in 2ml Administer 100mg in 0.4ml as a SUSPENSION Add 2.63ml WFI to 500mg vial to give 500mg in 3ml Administer 100mg in 0.6ml as a SOLUTION	3, 74
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Administer volumes over 0.5ml by subconjunctival injection at two sites.

DRUG : Aztreonam

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	100mg	Azactam	Add 2.1ml WFI to 500mg vial to give 500mg in 2.5ml Administer 100mg in 0.5ml	75
intravitreal injection	0.1mg	Azactam	Add 2.1ml WFI to 500mg vial to give 500mg in 2.5ml Dilute 1ml to 10ml with WFI to give 10mg in 10ml Administer 0.1mg in 0.1ml	75
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Azactam injection contains excipients.
Use to date has only been in experimental animals

DRUG : Bacitracin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	10,000 units	No commercial product available	Dilution should be made with WFI	9, 36 69, 73 76
intravitreal injection	500 - 1000 units	No commercial product available	Dilution should be made with WFI	69
intravitreal infusion			No information	
intracameral injection	500 - 1000 units	No commercial product available	Dilution should be made with WFI	36, 73 76
retrobulbar injection	---		No information	

COMMENTS :

DRUG : Benzylpenicillin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	300mg	Crystapen	Add 0.6ml Lignocaine with Adrenaline to 600mg vial to give 600mg in 1ml Administer 300mg in 0.5ml as a SUSPENSION Add 1.6ml Lignocaine with Adrenaline to 600mg vial to give 600mg in 2ml Administer 300mg in 1ml as a SOLUTION	8, 9 11, 30 36, 69 70, 73 76 - 81
intravitreal injection	1.2mg	Crystapen	Add 1.05ml WFI to 300mg vial to give 300mg in 1.25ml. Dilute 0.1ml to 2ml with WFI to give 12mg in 1ml Administer 1.2mg in 0.1ml	9, 11 33, 69 82
intravitreal infusion	10 microg /ml	Crystapen	Add 4.8ml WFI to 300mg vial to give 300mg in 5ml Dilute 0.08ml to 500ml with vitrectomy infusion fluid to give 10 micrograms / ml	9, 37 38
intracameral injection	3mg	Crystapen	Add 4.8ml WFI to 300mg vial to give 300mg in 5ml Dilute 1ml to 2ml with WFI to give 60mg in 2ml Administer 3mg in 0.1ml	10, 11 36, 73 76
retrobulbar injection			No information	

COMMENTS : Subconjunctival injection is an indication recognised by the manufacturer. For Lignocaine with Adrenaline use Lignocaine 2% with Adrenaline 1 in 100,000 or 1 in 80,000. For vitrectomy infusion fluid use Balanced Salt Solution isotonic with ocular tissues, Hartmann's Solution or Ringers Solution. Administer volumes over 0.5ml by subconjunctival injection at two sites.

DRUG : Betamethasone

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	2 - 4mg	Betnesol	Commercially available injection containing 4mg/ml Administer 2mg in 0.5ml	36,83
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Subconjunctival injection is an indication recognised by the manufacturer

DRUG : Carbenicillin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	125mg	Pyopen	Add 3.25ml Lignocaine with Adrenaline to 1g vial to give 1g in 4ml Administer 125mg in 0.5ml	9, 21 30, 36 69, 81 84 - 86
intravitreal injection	2mg	Pyopen	Add 1.25ml WFI to 1g vial to give 1g in 2ml Dilute 0.1ml to 2.5ml with WFI to give 20mg in 1ml Administer 2mg in 0.1ml	9, 10 36, 38 62, 69 84, 86 87
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Subconjunctival injection is an indication recognised by the manufacturer. For Lignocaine with Adrenaline use Lignocaine 2% with Adrenaline 1 in 100,000 or 1 in 80,000.

DRUG : Cefotaxime

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	50 - 100mg	Claforan	Add 1.8ml WFI to 500mg vial to give 500mg in 2.5ml Administer 50mg in 0.25ml to 100mg in 0.5ml	4, 88 89
intravitreal injection	0.4mg	Claforan	Add 4.3ml WFI to 500mg vial to give 500mg in 5ml. Dilute 0.4ml to 10ml with WFI to give 4mg in 1ml Administer 0.4mg in 0.1ml	84
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS:

DRUG : Cefoxitin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection			No information	
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS :

DRUG : Cefsulodin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	50mg	Monaspor	Add 4.675ml WFI to 500mg vial to give 500mg in 5ml Administer 50mg in 0.5ml	5, 20 90
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS :

DRUG : Ceftazidime

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	125mg	Fortum	Add 0.84ml WFI to 250mg vial to give 250mg in 1ml Administer 125mg in 0.5ml	91, 92
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : On reconstitution the solution is effervescent and should be allowed to stand before use

DRUG : Cefuroxime

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	100mg	Zinacef	Add 0.82ml WFI to 250mg vial to give 250mg in 1ml Administer 100mg in 0.4ml as a SUSPENSION Add 1.82ml WFI to 250mg vial to give 250mg in 2ml Administer 100mg in 0.8ml as a SOLUTION	36
intravitreal injection	2.5mg	Zinacef	Add 0.82ml WFI to 250mg vial to give 250mg in 1ml Dilute 0.1ml to 1ml with WFI to give 25mg in 1ml Administer 2.5mg in 0.1ml	93, 94
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : The suspension mentioned is rather viscous and may require use of a larger gauge needle. Administer volumes over 0.5ml by subconjunctival injection at two sites.

DRUG : Cephaloridine

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	100mg	No commercial product available	Dilution should be made with WFI	69
intravitreal injection	0.25mg	No commercial product available	Dilution should be made with WFI	10, 62 69
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS :

DRUG : Cephalothin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	25 - 100mg	Keflin	Add 4.3ml WFI to 1g vial to give 1g in 5ml Administer 25mg in 0.125ml to 100mg in 0.5ml	9, 30 36, 95 96
intravitreal injection	2mg	Keflin	Add 9.3ml WFI to 1g vial to give 1g in 10ml Dilute 1ml to 5ml with WFI to give 20mg in 1ml Administer 2mg in 0.1ml	9, 30
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS :

DRUG : Cephamandole

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	12.5mg	Kefadol	Add 3.65ml WFI to 500mg vial to give 500mg in 4ml Administer 12.5mg in 0.1ml	1, 9 30, 81
intravitreal injection	0.25mg	Kefadol	Add 3.65ml WFI to 500mg vial to give 500mg in 4ml Dilute 0.2ml to 10ml to give 25mg in 10ml Administer 0.25mg in 0.1ml	97
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Kefadol contains excipients

DRUG : Cephazolin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	100mg	Kefzol	Add 2.2ml WFI to 500mg vial to give 500mg in 2.5ml Administer 100mg in 0.5ml	1, 9 36, 37 81, 86 90 98- 104
intravitreal injection	0.5 - 2mg	Kefzol	Add 2.2ml WFI to 500mg vial to give 500mg in 2.5ml Dilute 0.5ml to 10ml with WFI to give 100mg in 10ml Administer 1mg in 0.1ml	9, 18 36, 37 39, 55 72, 86 90, 100 103,105 106
intravitreal infusion			No information	
intracameral injection	0.25mg	Kefzol	Add 4.7ml WFI to 500mg vial to give 500mg in 5ml Dilute 0.25ml to 10ml with WFI to give 25mg in 10ml Administer 0.25mg in 0.1ml	36
retrobulbar injection			No information	

COMMENTS :

DRUG : Cephradine

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	50 - 100mg	Velosef	Add 4.6ml WFI to 500mg vial to give 500mg in 5ml Administer 50mg in 0.5ml to 100mg in 1ml	102,107
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Administer volumes over 0.5ml by subconjunctival injection at two sites.

DRUG : Chloramphenicol (not succinate ester)

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	100mg	No commercial product available Use locally available sterile intrathecal inj.	Dilution should be made with Lignocaine with Adrenaline	9, 30 36, 69 70, 73 76, 81 108,109
intravitreal injection	2mg	No commercial product available Use locally available sterile intrathecal inj.	Dilution should be made with WFI	9, 10 15, 36 38, 62 69
intravitreal infusion	10 microg /ml	No commercial product available Use locally available sterile intrathecal inj.	Dilution should be made with vitrectomy infusion fluid	9, 37 38
intracameral injection	1 - 4mg	No commercial product available Use locally available sterile intrathecal inj.	Dilution should be made with WFI	10, 36 76
retrobulbar injection			No information	

COMMENTS : All commercially available injectable products contain chloramphenicol succinate ester, which is normally activated by the liver. Although esterases are present in the eye it is not known whether these would hydrolyse sufficient chloramphenicol succinate. For Lignocaine with Adrenaline use Lignocaine 2% with Adrenaline 1 in 100,000 or 1 in 80,000. For vitrectomy infusion fluid use Balanced Salt Solution isotonic with ocular tissues, Hartmann's Solution or Ringers Solution

DRUG : Ciprofloxacin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	1mg	Ciproxin	Commercially available infusion containing 2mg/ml Administer 1mg in 0.5ml	110
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Use to date has only been in experimental animals

DRUG : Clindamycin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	15 - 40mg	Dalacin - C	Commercially available injection containing 150mg/ml Administer 15mg in 0.1ml to 40mg in 0.27ml	9, 30 36, 37 81 111-114
intravitreal injection	1mg	Dalacin - C	Dilute 0.1ml commercial injection to 1.5ml with normal saline to give 15mg in 1.5ml Administer 1mg in 0.1ml	9, 10 17, 38 62, 90 106
intravitreal infusion	9 microg /ml	Dalacin - C	Dilute 0.3ml commercial injection to 10ml with normal saline to give 4.5mg in 10ml Dilute 1ml to 500ml with vitrectomy infusion fluid to give 9 micrograms/ml	37, 38 97
intracameral injection			No information	
retrobulbar injection	75 - 150mg	Dalacin - C	Commercially available injection containing 150mg/ml Administer 75mg in 0.5ml to 150mg in 1ml	113

COMMENTS : For vitrectomy infusion fluid use Balanced Salt Solution isotonic with ocular tissues, Hartmann's Solution or Ringers Solution

DRUG : Clotrimazole

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	5 - 10mg	No commercial product available	Dilution should be made with Lignocaine with Adrenaline	115
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : For Lignocaine with Adrenaline use Lignocaine 2% with Adrenaline 1 in 100,000 or 1 in 80,000

DRUG : Cloxacillin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	100mg	Orbenin~	Add 0.8ml Lignocaine with Adrenaline to 250mg vial to give 250mg in 1ml Administer 100mg in 0.4ml	21, 36 116,117
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Although doses are quoted for cloxacillin it has been reported to cause corneal opacity and ulceration. For Lignocaine with Adrenaline use Lignocaine 2% with Adrenaline 1 in 100,000 or 1 in 80,000

DRUG : Co-trimoxazole

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection			No information	121
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Co-trimoxazole preparations are too irritant to be administered by these routes

DRUG : Colistin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	15 - 30mg	Colomycin	Add 2ml Lignocaine with Adrenaline to 1,000,000un vial to give 1,000,000 units (80mg) in 2ml Administer 15mg in 0.37ml to 30mg in 0.75ml	36, 69 76, 118 119
intravitreal injection	0.1mg	Colomycin	Add 2ml normal saline to 1,000,000 unit vial to give 1,000,000 units (80mg) in 2ml Dilute 0.25ml to 10ml with normal saline to give 10mg in 10ml Administer 0.1mg in 0.1ml	69
intravitreal infusion			No information	
intracameral injection	0.1mg	Colomycin	Add 2ml normal saline to 1,000,000 unit vial to give 1,000,000 units (80mg) in 2ml Dilute 0.25ml to 10ml with normal saline to give 10mg in 10ml Administer 0.1mg in 0.1ml	10, 36 73, 76 120
retrobulbar injection			No information	

COMMENTS : Subconjunctival injection is an indication recognised by the manufacturer
For Lignocaine with Adrenaline use Lignocaine 2% with Adrenaline 1 in 100,000 or 1 in 80,000

DRUG : Dexamethasone

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	2mg	Decadron	Commercially available injection containing 4mg/ml Administer 2mg in 0.5ml	36, 90 97, 122 123
intravitreal injection	0.4mg	Decadron	Commercially available injection containing 4mg/ml Administer 0.4mg in 0.1ml	18, 36 39, 103 106,124
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : The use of intravitreal corticosteroids has been reported to carry a risk of activating latent amebiasis and strongyloidiasis

DRUG : Econazole

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	5 - 10mg	No commercial product available	Dilution should be made with WFI	115
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS :

DRUG : Erythromycin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	25 - 50mg	Erythrocin IV Lactibionate	Add 15.6ml WFI to 1g vial to give 1g in 16ml Administer 25mg in 0.4ml to 100mg in 0.8ml	9, 30 36, 73 76
intravitreal injection	0.5mg	Erythrocin IV Lactibionate	Add 20ml WFI to 1g vial to give 50mg in 1ml Dilute 1ml to 10ml with WFI to give 5mg in 1ml Administer 0.5mg in 0.1ml	9, 10 30,36 38,62
intravitreal infusion			No information	
intracameral injection	1mg	Erythrocin IV Lactibionate	Add 20ml WFI to 1g vial to give 50mg in 1ml Dilute 1ml to 5ml with WFI to give 10mg in 1ml Administer 1mg in 0.1ml	10, 30 36, 73 76
retrobulbar injection			No information	

COMMENTS : The 1g vial of Erythrocin IV actually contains 1.1g. Administer volumes over 0.5ml by subconjunctival injection at two sites.

DRUG : Flucloxacillin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	100mg	Floxapen	Add 0.8ml Lignocaine with Adrenaline to 250mg vial to give 250mg in 1ml Administer 100mg in 0.4ml	36, 117
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Although doses are quoted for flucloxacillin it has been reported to cause corneal opacity and ulceraction. For Lignocaine with Adrenaline use Lignocaine 2% with Adrenaline 1 in 100,000 or 1 in 80,000

DRUG : Flucytosine

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	2.5mg	Alcobon	Commercially available infusion containing 10mg/ml Administer 2.5mg in 0.25ml	51, 66 125
intravitreal injection	0.2mg	Alcobon	Commercially available injection to 5ml with WFI to give 10mg in 5ml Administer 200 micrograms in 0.1ml	48
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Alcobon contains excipients

DRUG : Fluorouracil

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	10mg	Fluoro-Uracil	Commercially available injection containing 25mg/ml Administer 10mg in 0.4ml	126
intravitreal injection	1mg	Fluoro-Uracil	Dilute 0.4ml commercial injection to 1ml with normal saline to give 10mg in 1ml Administer 1mg in 0.1ml	126
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Fluorouracil is used in the treatment of complicated retinal detachment

DRUG : Foscarnet

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection			No information	170
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Foscarnet is too irritant for administration by these routes

DRUG : Framycetin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	100 - 500mg	Soframycin Sterile Powder	Add 0.5ml WFI to 500mg vial to give 500mg in 0.5ml Administer 100mg in 0.1ml to 500mg in 0.5ml	11, 36 73, 76 79 127-133
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Subconjunctival injection is an indication recognised by the manufacturer
Intravitreal injection of framycetin has been linked with prolonged curarization

DRUG : Ganciclovir

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	1.25mg	Cymevene	Add 9.71ml WFI to 500mg vial to give 500mg in 10ml Dilute 0.5ml to 10ml with WFI to give 25mg in 10ml Administer 1.25mg in 0.5ml	134,135
intravitreal injection	0.2mg	Cymevene	Add 9.71ml WFI to 500mg vial to give 500mg in 10ml Dilute 0.4ml to 10ml with WFI to give 20mg in 10ml Administer 0.2mg in 0.1ml	134-144
intravitreal infusion	30 microg /ml	Cymevene	Add 9.71ml WFI to 500mg vial to give 500mg in 10ml Dilute 0.3ml to 500ml with vitrectomy infusion fluid to give 30 micrograms/ml	145
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : The use of ganciclovir by subconjunctival injection may be irritant due to the injection being pH 11. Use by this route has been mainly in experimental animals. For vitrectomy infusion fluid use Balanced Salt Solution isotonic with ocular tissues, Hartmann's Solution or Ringers Solution

DRUG : Gentamicin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	10 - 20mg	Gentamicin BP single dose with - out preservative (DBL)	Commercially available injection containing 40mg/ml Administer 10mg in 0.25ml to 20mg in 0.5ml	1,9,11 12,36,37 43,48,69 81,84,86 90,100 102,103 105, 146-152
intravitreal injection	0.1 - 0.2mg	Cidomycin Powder Genticin Powder	Use Cidomycin Sterile or Genticin Pure Powder Add 10ml WFI to 1g vial to give 100mg in 1ml For 0.1mg dilute 0.1ml to 10ml with WFI to give 1mg in 1ml For 0.2mg dilute 0.2ml to 10ml with WFI to give 2mg in 1ml Administer 0.1ml	9, 10 11, 18 36 - 38 41, 55 62, 69 84, 86 90, 97 100,103 106 153-155
		Cidomycin Intrathecal	Use Cidomycin Intrathecal injection containing 5mg/ml For 0.1mg dilute 0.2ml to 1ml with WFI to give 1mg in 1ml For 0.2mg dilute 0.4ml to 1ml with WFI to give 2mg in 1ml Administer 0.1ml	
intravitreal infusion	8mcg/ml	Cidomycin Intrathecal	Dilute 0.8ml commercial injection to 500ml with vitrectomy infusion fluid to give 8 micrograms/ml	9, 37 38, 90 97
intracameral injection	0.1 - 0.2mg	Cidomycin Powder Cidomycin Intrathecal Genticin Powder	As intravitreal injection	11, 36 37
retrobulbar injection	5mg	Gentamicin BP single dose with - out preservative (DBL)	Dilute 2.5ml commercial injection to 10ml with WFI to give 100mg in 10ml Administer 5mg in 0.5ml	12, 156

COMMENTS : Subconjunctival and intravitreal injection are indications recognised by the manufacturer. For vitrectomy infusion fluid use Balanced Salt Solution isotonic with ocular tissues, Hartmann's Solution or Ringers Solution

DRUG : Isoniazid

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	10 - 20mg	Rimifon	Commercially available injection containing 25mg/ml Administer 10mg in 0.4ml to 20mg in 0.8ml	30
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Rimifon contains excipients. Administer volumes over 0.5ml by subconjunctival injection at two sites.

DRUG : Kanamycin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	10 - 20mg	Kannasyn Sterile Powder	Add 3.2ml WFI to 1g vial to give 1g in 4ml Dilute 1ml to 5ml with WFI to give 50mg in 1ml Administer 10mg in 0.2ml to 20mg in 0.4ml	36, 73 76
intravitreal injection	0.5mg	Kannasyn Sterile Powder	Add 3.2ml WFI to 1g vial to give 1g in 4ml Dilute 0.2ml to 10ml with WFI to give 5mg in 1ml Administer 0.5mg in 0.1ml	10, 38 62
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS :

DRUG : Latamoxef

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	100mg	Moxalactam	Add 2.1ml WFI to 500mg vial to give 500mg in 2.5ml Administer 100mg in 0.5ml	9
intravitreal injection	2mg	Moxalactam	Add 2.1ml WFI to 500mg vial to give 500mg in 2.5ml Dilute 0.1ml to 1ml with WFI to give 20mg in 1ml Administer 2mg in 0.1ml	9
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Moxalactam contains excipients

DRUG : Lincomycin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	75 - 150mg	Lincocin	Commercially available injection containing 300mg/ml Administer 75mg in 0.25ml to 150mg in 0.5ml	5, 36
intravitreal injection	1.5mg	Lincocin	Dilute 0.1ml commercial injection to 2ml with normal saline to give 30mg in 2ml Administer 1.5mg in 0.1ml	16,36 38
intravitreal infusion	10 microg /ml	Lincocin	Dilute 0.16ml commercial injection to 10ml with normal saline to give 50mg in 10ml Dilute 1ml to 500ml with vitrectomy infusion fluid to give 10 micrograms/ml	37
intracameral injection	1.5mg	Lincocin	Dilute 0.1ml commercial injection to 2ml with normal saline to give 30mg in 2ml Administer 1.5mg in 0.1ml	36
retrobulbar injection			No information	

COMMENTS : For vitrectomy infusion fluid use Balanced Salt Solution isotonic with ocular tissues, Hartmann's Solution of Ringers Solution

DRUG : Methicillin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	100 - 500mg	Celbenin	Add 1.3ml WFI to 1g vial to give 1g in 2ml Administer 100mg in 0.2ml to 500mg in 1ml	9, 11 21, 36 62, 69 71, 73 76, 81 157,158
intravitreal injection	2mg	Celbenin	Add 4.3ml WFI to 1g vial to give 1g in 5ml. Dilute 1ml to 10ml with WFI to give 20mg in 1ml Administer 2mg in 0.1ml	9, 10 30, 36 38, 55 69
intravitreal infusion	20 microg /ml	Celbenin	Add 4.3ml WFI to 1g vial to give 1g in 5ml Dilute 0.05ml to 500ml with vitrectomy infusion fluid to give 20 micrograms/ml	9, 37 38
intracameral injection	1.5mg	Celbenin	Add 4.3ml WFI to 1g vial to give 1g in 5ml. Dilute 0.75ml to 10ml with WFI to give 15mg in 1ml Administer 1.5mg in 0.1ml	10, 36 76
retrobulbar injection			No information	

COMMENTS : Subconjunctival injection is an indication recognised by the manufacturer. For vitrectomy infusion fluid use Balanced Salt Solution isotonic with ocular tissues, Hartmann's Solution or Ringers Solution. Administer volumes over 0.5ml by subconjunctival injection at two sites.

DRUG : Methylprednisolone

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	20 - 40mg	Depo - Medrone	Commercially available injection containing 40mg/ml Administer 20mg in 0.5ml to 40mg in 1ml	36, 46 159,160
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection	20mg	Depo - Medrone	Commercially available injection containing 40mg/ml Administer 20mg in 0.5ml	160

COMMENTS : Administer volumes over 0.5ml by subconjunctival injection at two sites.

DRUG : Mezlocillin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	100mg	Baypen	Add 2.63ml WFI to 500mg vial to give 500mg in 3ml Administer 100mg in 0.6ml	6, 74
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Administer volumes over 0.5ml by subconjunctival injection at two sites.

DRUG : Miconazole

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	5mg	Daktarin	Commercially available injection containing 10mg/ml Administer 5mg in 0.5ml	30, 48 67, 101 115 161-163
intravitreal injection	20 microg	Daktarin	Dilute 0.2ml commercial injection to 10ml with normal saline to give 0.2mg in 1ml Administer 20 micrograms in 0.1ml	9, 55 164,165
intravitreal infusion			No information	
intracameral injection	10 microg	Daktarin	Dilute 0.1ml commercial injection to 10ml with normal saline to give 0.1mg in 1ml Administer 10 micrograms in 0.1ml	48
retrobulbar injection			No information	

COMMENTS :

DRUG : Natamycin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection			No information	30, 66
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : The use of natamycin by these routes has been reported to cause necrosis

DRUG : Neomycin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	100 - 500mg	Mycifradin Sterile Powder	Add 1ml WFI to 500mg vial to give 500mg in 1ml Administer 100mg in 0.2ml to 500mg in 1ml	9, 11 69, 73 76
intravitreal injection	2.5mg	Mycifradin Sterile Powder	Add 5ml normal saline to 500mg vial to give 500mg in 5ml. Dilute 1ml to 4ml with normal saline to give 100mg in 4ml Administer 2.5mg in 0.1ml	69
intravitreal infusion			No information	
intracameral injection	2.5mg	Mycifradin Sterile Powder	Add 5ml normal saline to 500mg vial to give 500mg in 5ml. Dilute 1ml to 4ml with normal saline to give 100mg in 4ml Administer 2.5mg in 0.1ml	10, 11 36, 73 76
retrobulbar injection			No information	

COMMENTS : Mycifradin Sterile Powder is now discontinued. Subconjunctival injection of neomycin is painful. Administer volumes over 0.5ml by subconjunctival injection at two sites.

DRUG : Netilmicin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	10 - 20mg	Netillin	Commercially available injection containing 50mg/ml Administer 10mg in 0.2ml to 20mg in 0.4ml	9, 166 167,168
intravitreal injection	0.25mg	Netillin	Commercially available injection containing 10mg/ml Dilute 2.5ml to 10ml to give 25mg in 10ml Administer 0.25mg in 0.1ml	9, 40 51,168
intravitreal infusion	10 microg /ml	Netillin	Dilute 0.5ml commercial injection containg 10mg/ml to 500ml with vitrectomy infusion fluid to give 10 micrograms/ml	9, 38
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Netillin injection contains excipients. For vitrectomy infusion fluid use Balanced Salt Solution isotonic with ocular tissues, Hartmann's Solution or Ringers Solution.

DRUG : Novobiocin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	12.5mg	No commercial product available	Dilution should be made with WFI	30, 73 76
intravitreal injection	0.1mg	No commercial product available	Dilution should be made with WFI	30
intravitreal infusion			No information	
intracameral injection	0.25mg	No commercial product available	Dilution should be made with WFI	30
retrobulbar injection			No information	

COMMENTS :

DRUG : Nystatin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	5000 units	Mycostatin Sterile Powder	Add 10ml normal saline to 500,000 unit vial to give 50,000 units in 1ml Dilute 1ml to 5ml with normal saline to give 10,000 units in 1ml Administer 5,000 units in 0.5ml	30, 44 49, 52 53, 61 169
intravitreal injection	200 units	Mycostatin Sterile Powder	Add 10ml normal saline to 500,000 unit vial to give 50,000 units in 1ml Dilute 0.2ml to 5ml with normal saline to give 2000 units in 1ml Administer 200 units in 0.1ml	49, 52 169
intravitreal infusion			No information	
intracameral injection	200 units	Mycostatin Sterile Powder	Add 10ml normal saline to 500,000 unit vial to give 50,000 units in 1ml Dilute 0.2ml to 5ml with normal saline to give 2000 units in 1ml Administer 200 units in 0.1ml	52
retrobulbar injection			No information	

COMMENTS :

DRUG : Piperacillin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	100mg	Pipril	Add 4.27ml WFI to 1g vial to give 1g in 5ml Administer 100mg in 0.5ml	9, 84
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS :

DRUG : Polymixin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	10mg	Aerosporin	Add 1ml Lignocaine with Adrenaline to 50mg vial to give 50mg in 1ml Administer 10mg in 0.2ml	9, 30 36, 69 73, 76 79, 119 171-174
intravitreal injection	0.1mg	Aerosporin	Add 1ml WFI to 50mg vial to give 50mg in 1ml Dilute 0.2ml to 10ml with WFI to give 10mg in 10ml Administer 0.1mg in 0.1ml	69
intravitreal infusion			No information	
intracameral injection	0.1mg	Aerosporin	Add 1ml WFI to 50mg vial to give 50mg in 1ml Dilute 0.2ml to 10ml with WFI to give 10mg in 10ml Administer 0.1mg in 0.1ml	10, 36 76
retrobulbar injection			No information	

COMMENTS : 50mg is equivalent to 500,000 units. Subconjunctival injection is an indication recognised by the manufacturer. For Lignocaine with Adrenaline use Lignocaine 2% with Adrenaline 1 in 100,000 or 1 in 80,000.

DRUG : Pyrimethamine

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	50 microg	No commercial product available	Dilution should be made with WFI	9, 30
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS :

DRUG : Sodium Fusidate

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection			No information	175,176
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Sodium Fusidate is reported to cause corneal oedema and necrosis when administered by these routes

DRUG : Streptomycin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	50 - 100mg	Streptomycin Inj. (Evans)	Add 4.25ml Lignocaine with Adrenaline to 1g vial to give 1g in 5ml Administer 50mg in 0.25ml to 100mg in 0.5ml	10, 36 70, 73 76, 80 81, 173
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection	2.5mg	Streptomycin Inj. (Evans)	Add 4.25ml WFI to 1g vial to give 1g in 5ml Dilute 1.25ml to 10ml with WFI to give 250mg in 10ml Administer 2.5mg in 0.1ml	10, 36 73, 76
retrobulbar injection			No information	

COMMENTS : For Lignocaine with Adrenaline use Lignocaine 2% with Adrenaline 1 in 100,000 or 1 in 80,000.

DRUG : Tetracycline

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	2.5 - 5mg	Achromycin IV	Add 5ml WFI to 250mg vial to give 250mg in 5ml Dilute 1ml to 5ml with WFI to give 50mg in 5ml Administer 2.5mg in 0.25ml to 5mg in 0.5ml	73, 76
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection	2.5 - 5mg	Achromycin IV	Add 5ml WFI to 250mg vial to give 250mg in 5ml Dilute 1ml to 5ml with WFI to give 50mg in 5ml Administer 2.5mg in 0.25ml to 5mg in 0.5ml	10, 36 73, 76
retrobulbar injection			No information	

COMMENTS : Achromycin contains excipients

DRUG : Ticarcillin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	100mg	Ticar	Add 3.3ml WFI to 1g vial to give 1g in 4ml Administer 100mg in 0.4ml	9, 36
intravitreal injection			No information	
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS :

DRUG : Tobramycin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	10 - 20mg	Nebcin	Commercially available injection containing 40mg/ml Administer 10mg in 0.25ml to 20mg in 0.5ml	7, 9 11, 30 36, 69 86, 90 177,178
intravitreal injection	0.1 - 0.4mg	Nebcin	For 0.1mg dilute 0.25ml commercial injection to 10ml with WFI to give 10mg in 10ml For 0.4mg dilute 1ml commercial injection to 10ml with WFI to give 40mg in 10ml Adminster 0.1ml	9, 10 38, 62 69, 86
intravitreal infusion	10 microg /ml	Nebcin Paediatric	Dilute 0.5ml commercial injection to 500ml with vitrectomy infusion fluid to give 10 micrograms/ml	9, 10 38
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Nebcin contains excipients. For vitrectomy infusion fluid use Balanced Salt Solution isotonic with ocular tissues, Hartmann's Solution or Ringers Solution.

DRUG : Triamcinolone

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	20 - 40mg	Kenalog	Commercially available injection containing 40mg/ml Administer 20mg in 0.5ml	48, 179 180
intravitreal injection	1mg	Kenalog	Dilute 2.5ml commercial injection to 10ml with WFI to give 100mg in 10ml Administer 1mg in 0.1ml	159
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : The use of intravitreal corticosteroids has been reported to carry a risk of activating latent amebiasis and strongyloidiasis

DRUG : Vancomycin

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	25mg	Vancocin	Add 9.7ml Lignocaine with Adrenaline to 500mg vial to give 500mg in 10ml Administer 25mg in 0.5ml	9, 30 36, 69 86
intravitreal injection	1mg	Vancocin	Add 9.7ml WFI to 500mg vial to give 500mg in 10ml Dilute 1ml to 5ml with WFI to give 10mg in 1ml Administer 1mg in 0.1ml	38, 41 55, 86 181
intravitreal infusion			No information	
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : The use of vancomycin by subconjunctival injection may be irritant due to the injection being pH 2.5. For Lignocaine with Adrenaline use Lignocaine 2% with Adrenaline 1 in 100,000 or 1 in 80,000.

DRUG : Vidarabine

ROUTE	DOSE	BRAND	METHOD OF PREPARATION	Refs
subconjunctival injection	50mg	Vira - A	Commercially available injection containing 200mg/ml Administer 50mg in 0.25ml	9, 182
intravitreal injection	40 microg	Vira - A	Dilute 0.1ml commercial injection to 50ml with WFI to give 20mg in 50ml Administer 40 micrograms in 0.1ml	9, 32 33
intravitreal infusion	8 microg /ml	Vira - A	Dilute 0.2ml commercial injection to 10ml with WFI to give 40mg in 10ml Dilute 1ml to 500ml with vitrectomy infusion fluid to give 8 micrograms/ml	9, 32
intracameral injection			No information	
retrobulbar injection			No information	

COMMENTS : Vira - A contains excipients. For vitrectomy infusion fluid use Balanced Salt Solution isotonic with ocular tissues, Hartmann's Solution or Ringers Solution.

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184. Personal Communication with Pharmaceutical Manufacturers

DISPLACEMENT VOLUMES

It may be necessary to prepare these injections from a vial of a different size to that which is recommended in the method of preparation. Therefore displacement volumes have been included to allow ease of calculation. (183, 184)

Drug	Brand	Displacement Volume ml / g
Amoxycillin	Amoxil	0.80
Ampicillin	Penbritin	0.80
Azlocillin	Securopen	0.74
Aztreonam	Azactam	0.80
Benzylpenicillin	Crystapen	0.67
Carbenicillin	Pyopen	0.75
Cefotaxime	Claforan	0.40
Cefsulodin	Monaspor	0.65
Ceftazidime	Fortum	0.65
Cefuroxime	Zinacef	0.72
Cephalothin	Keflin	0.70
Cephamandole	Kefadol	0.70
Cefazolin	Kefzol	0.60
Cephradine	Velosef	0.80
Cloxacillin	Orbenin	0.80
Erythromycin	Erythrocin	1.82
Flucloxacillin	Floxapen	0.80
Ganciclovir	Cymevene	0.58
Kanamycin	Kannasyn	0.80
Latamoxef	Moxalactam	0.80
Methicillin	Celbenin	0.70
Mezlocillin	Baypen	0.74
Piperacillin	Pipril	0.73
Streptomycin	Evans	0.75
Ticarcillin	Ticar	0.70
Vancomycin	Vancocin	0.60

INDEX

NOTES

87

NOTES

88

89

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