2.1 Introduction

Drug delivery can make a big difference in ocular drug treatment. From the drug delivery point of view the eye is a very interesting small multicompartmental system with various tissues, their boundaries and fluid flow factors. The isolation of the vitreous caused by the blood-retinal and blood-aqueous barriers creates difficulties for effective drug therapy in all eye diseases [1]. Systemic administration is often not feasible because only a small percentage of drugs can penetrate the ophthalmic barriers and their pharmacokinetics are complicated by the fast flowing blood supply in the posterior segment of the eye [2]. Thus large systemic doses are needed to achieve therapeutic concentrations in ocular tissues, which cause problems such as unwanted side effects and potential toxicity from the drug. Therefore, regardless of the dosage form and constituents thereof, the most common route of drug delivery to the eye is topical.

Local administration remains the mainstay of ocular drug treatment unless highly selective drug targeting systems are developed. Designing and formulating ocular delivery systems for topically applied ophthalmic drugs is very intricate and requires a thorough understanding of the physiological basis of the protective mechanisms of the eye that restrict the bioavailability of the topically applied dose to less than 10%. Topical delivery into the cul-de-sac is the most common route of ocular drug delivery and is considered to be the preferred way to achieve therapeutic levels of drug agents used to treat ocular diseases. Drugs applied topically are absorbed from the cul-de-sac either by the corneal or by the noncorneal pathway. Drug absorption by the noncorneal route involves penetration across the sclera and conjunctiva into the intraocular tissues. This route of drug absorption prevents the entry of the drug into the aqueous humour as the drug penetrating the surface of the eye beyond the corneal scleral limbus is picked up by local capillary beds and is then removed to the general circulation. This route of drug absorption is significant for drugs which are absorbed poorly by the cornea; however for most therapeutic agents, the major mechanism of ocular absorption is corneal absorption.
Ophthalmic drug delivery serves as a vehicle for the administration of wide ranges of drugs. The literature reveals that the earliest ocular treatment dates back to the Mesopotamian era. One of the first therapeutic delivery systems is noted in the writings of Celsus (20 BC - AD 50). It was developed by the Romans and named ‘Collyrium’ [3]. The term ‘belladonna’ (or ‘beautiful lady’) evolved during the ‘middle ages’ from such collyria, which contained components to dilate the pupils of a lady’s eyes for cosmetic purposes [4]. The collyria gave rise to modern day eye drop solutions. However, improvement in ocular delivery preparations and treatment did not happen for many centuries until the seventeenth century and then ocular therapeutics became meaningful.

Prior to World War II and well into the 1940s, most solutions for eye use were compounded by the pharmacist in the community pharmacy and were intended for immediate use, perhaps due to an unconfirmed stability of the drug [4]. The availability of such solutions in a sterile dosage form marked the most important milestone in the twentieth century for the modern day eye drop solution. Alcon Pharmacy (currently known as Alcon Laboratories Inc.), a dispensing pharmacy during the day and a manufacturing pharmacy during the night, was the first provider of sterile ophthalmic solutions in 1947, long before the Food and Drug Administration adopted the position in 1953 that a nonsterile ophthalmic solution was considered to be adulterated. Subsequently the United States Pharmacopoeia (USP) adopted sterility as a requirement for ophthalmic solutions in 1955 [5].

Ophthalmic preparations are similar to parenteral dosage forms in their requirement for sterility as well as consideration for tonicity, preservation, tissue compatibility, the avoidance of pyrogens and particulate matter in the formulation, and suitable packaging of the dosage form [6]. The formulation of stable, therapeutically active ophthalmic preparations requires a high purity of ingredients as well as freedom from chemical, physical and microbial contaminants. Ocular preparations usually require buffers to stabilise the pH of the products, additives to render them isotonic or nearly so, and stabilisers such as antioxidants when appropriate for particular ingredients.

The conventional preparations used in the ocular route fall into two categories, namely eye drops and semisolid dosage forms. The two major physical forms of eye drops are aqueous solutions and suspensions. The principal semisolid dosage form used in ophthalmology is an anhydrous ointment with a petrolatum base. It is usual that water soluble drugs are delivered through topical administration in an aqueous solution and water insoluble drugs are administered topically as an aqueous suspension or ointment. The major deficiencies of the conventional dosage forms include poor ocular drug bioavailability, pulse drug entry after topical administration, systemic exposure because of nasolachrymal duct drainage and a lack of effective systems for drug delivery to the posterior segment of ocular tissue. Still, these formulations remain universally used in the management of ocular diseases as conventional ophthalmic
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dosage forms are simple to formulate and simple for patients to use. The following section deals in brief with conventional ocular dosage forms. As more details do not fall within the scope of this book, interested readers can refer to the literature covering the different aspects of these formulations in depth [7-9].

2.2 Eye Drops

Although many alternative experimental methods have been tried, the use of eye drops remains the major method of administration for the topical ocular route. These are by far the most common dosage forms for delivering drugs to the eye and are one of the few dosage forms not administered by exact volume or weight dosage, yet this apparently imprecise method of dosing is quite well-established and accepted by the ophthalmologist.

2.2.1 Aqueous Solutions

Most of the topical ophthalmic preparations available today are in the form of aqueous solutions. By definition, the ingredients are completely soluble so that dose uniformity is not an issue and there is little physical interference with vision. Almost all ophthalmic therapeutic agents are water soluble or can be formulated as water soluble salts. Aqueous solutions are easy to manufacture and they assure greater uniformity of dosage and bioavailability. Drugs that have limited stability in liquid form are prepared as sterile powders for reconstitution. A homogeneous solution dosage form offers many advantages including the simplicity of large scale manufacture. Selection of the appropriate salt of the drug substance, solubility, therapeutic concentration required, ocular toxicity, pKa, the effect of pH on stability and solubility, tonicity, buffer capacity, viscosity, compatibility with other formulation ingredients as well as packaging components, choice of preservative, ocular comfort and ease of manufacturing are the factors that the formulator must consider while formulating aqueous solutions.

The manufacturing of ophthalmic dosage forms including solutions must meet certain safety criteria including freedom from extraneous foreign particulate matter and the efficacy, safety and stability of the therapeutic agent. Current United States standards of good manufacturing practice (GMP) provide for the use of specially designed, environmentally controlled areas for the manufacture of sterile ophthalmic products and these design criteria are often coupled with laminar airflow concepts. The area where open containers and closures are exposed must meet the requirements of Class 100 (GMP) and in all the areas where open containers and closures are not exposed, or where product filling and capping are not taking place, must follow Class 100,000 (GMP). Additionally, the materials used for construction of the facility and
for personnel attire, training, conduct in the space, and the entrance and egress of personnel, equipment, packaging and product are all important for the assurance of product sterility and minimisation of foreign particulate matter.

In general, aqueous ophthalmic solutions are manufactured by simply dissolving the active ingredient and other inactive ingredients in the aqueous medium and then sterilising the final solution by heat or by membrane filtration. Further, this sterile solution may be mixed with additional components such as previously sterilised solutions of viscosity modifying agents and then the final volume of the batch is made up with additional sterile water. The choice of pH for the formulations is a key attribute for the efficacy as the solubility, stability and corneal permeability of the drugs depend on this parameter. Quite often, the pH of the preparation is a best possible compromise between stability and bioavailability. Additionally, ocular comfort must be kept in mind before finalising the pH of the dosage form. In general, a pH of 4.0-8.0 is preferred for ophthalmic solutions as eye irritation or ocular discomfort may become an issue if the pH is outside the physiological range [10]. Eye irritation is normally accompanied by an increase in fluid secretion to aid the restoration of normal physiological conditions that may eventually result in rapid flushing of the drug to the nasolachrymal duct with a probable influence on the ocular efficacy. Besides pH, proper choices of buffer and buffer capacity are essential to optimise drug bioavailability as well as ocular comfort.

An antimicrobial preservative is another important ingredient in typical multidose ophthalmic products and its primary purpose is to prevent the patient from administering microbiologically contaminated product into the eye. When selecting the antimicrobial preservative, the formulator must look for one that is effective at a low concentration against a broad spectrum of organisms, soluble in the formulation, compatible with the drug packaging components and effective over the shelf life. The limited number of preservatives available has presented problems of compatibility and pH stability for the formulator. For the most part, only three preservatives (benzalkonium chloride, thimerosal and chlorobutanol) are in common use, although mixtures and enhancers, such as ethylenediaminetetraacetic acid, have increased the spectrum of possibilities [11].

All raw materials used in the compounding of ophthalmic pharmaceutical products must be of the highest quality available. Every ingredient used in an ophthalmic preparation must be tested against multiple pharmacopoeial specifications to meet global requirements. In eye drops, the largest component is water and with few exceptions, aqueous fluids use purified water (USP) as the solvent. This can be obtained by distillation, deionisation or reverse osmosis. Sometimes, oils are used as vehicles for extremely moisture sensitive drugs. When oils are used as vehicles in ophthalmic fluids, they must be of the highest purity.
The principal disadvantage of solutions is their relatively brief contact time between the drug and the absorbing tissue of the external eye. Pulse entry is a common, yet highly undesirable, pharmacokinetic characteristic associated with aqueous solutions. The initial high drug concentration found in tears, followed by a rapid decline, poses a potential risk of toxicity and results in a requirement for frequent dosing.

2.2.2 Ophthalmic Suspensions

The traditional era of the solution-only dosage form for use in the eye ended in the 1950s with the availability of suspension dosage forms. Solid drug particles of cortisone acetate were suspended and the first suspension product was commercialised. In an unorthodox approach, clinical studies revealed for the first time that a drug with a sufficiently reduced particle size could be instilled onto ocular surfaces. This resulted in the availability of water insoluble or sparingly soluble drugs in suspension dosage forms for the treatment of ophthalmic disorders. The successful experimentation of delivering sparingly soluble drugs in a suspended form led the way for products with added values beyond simple presentations.

Suspensions form an important part of the ophthalmic dosage forms and offer distinct advantages. Suspensions are dispersions of finely divided, relatively insoluble drug substances in an aqueous vehicle containing suitable suspending and dispersing agents. Increasing awareness of the basic properties of drug molecules and the widespread availability of excipients promoted formulation and development scientists to develop ophthalmic suspensions for those drugs which have proven therapeutic activity but their application in ocular delivery is restricted due to their solubility problems. Many of the recently developed drugs are hydrophobic so have limited solubility in water and sometimes, a suspension is even formulated to improve the stability, bioavailability or efficacy of the therapeutic agent.

Formulation of a sterile, preserved, effective, stable and pharmaceutically elegant suspension is more complex and challenging compared to conventional ophthalmic solutions. The drug is present in micronised form and, generally, 95% or more of the particles have a diameter of 10 µm or less suspended in a suitable aqueous vehicle [12]. This particle size is required to ensure that the suspension does not lead to irritation of the sensitive ocular tissues and that a uniform dosage is delivered to the eye. The drug is absorbed from solution and the solution concentration is replenished from retained particles. Each of these actions is a function of particle size, with the solubility rate being favoured by smaller size; thus optimum activity should result from an optimum particle size. A particle size less than 10 µm is found to minimise the potential irritation to the eye; however other factors such as particle concentration, density and shape may also contribute to the comfort threshold of the patient [3].
Because of the tendency for the particles to be retained in the cul-de-sac, the contact time and duration of action of a suspension exceed those of a solution [13]. While the retention increases with an increase in the particle size, as does the irritation of the eye, the rate of dissolution of the suspended drugs increases with decreasing particle size. Thus, an optimum particle size has to be selected for each therapeutic agent.

The formulator must be aware of two potential difficulties inherent in suspension dosage forms. In the first instance, brisk shaking is nearly always required in order to distribute the suspended drug and ensure dosage uniformity. Adequate shaking is not only a function of the suitability of the suspension formulation but also, and most importantly, depends on patient compliance. A second and uncommon characteristic of suspensions is the phenomenon of polymorphism, or the ability of substance to exist in several different crystalline forms. A change in crystal structure may occur during storage thereby resulting in an increase or decrease in crystal size and alteration in suspension characteristics, causing solubility changes reflected in increased or decreased bioavailability. Most of the suspension products carry a ‘Do not freeze’ warning on the label as they are likely to agglomerate on freezing and may not be resuspended by simple shaking.

Pharmaceutical formulators developed an improved suspension to overcome the inherent problems of poor physical stability and patient-perceived discomfort. This improved suspension formulation controls the flocculation of the insoluble active ingredient particles so that they remain suspended for a prolonged period of time and any settled particles can be easily resuspended with only gentle shaking. In some cases, to extend the practical shelf life or to improve the bioavailability of a drug or patient tolerance, a water soluble drug is converted into an insoluble form to formulate an ophthalmic suspension. Steroids such as prednisolone and dexamethasone are the best examples of this approach. The insoluble forms of these drugs have better ocular bioavailability and are considered to be more potent anti-inflammatories for topical ocular use than their water soluble analogues [6].

An ophthalmic suspension contains many inactive ingredients such as dispersing and wetting agents, suspending agents, buffers and preservatives. Wetting agents are surfactants that are required to lower the contact angle between the solid surface and the wetting liquid. The wetting and solubilising agents which are generally used include Tweens (Polysorbate 20, Polysorbate 40, Polysorbate 60, Polysorbate 80), Spans (sorbitan monolaurate, sorbitan mono-oleate, sorbitan monopalmitate) and sodium lauryl sulfate.

Suspending agents are added to the suspension formulation to prevent sedimentation by affecting the rheological behaviour of a suspension. An ideal suspending agent should produce a structured vehicle, should be compatible with other formulation
ingredients and should be nontoxic. Suspending agents generally used in ophthalmic suspensions include cellulosic derivatives such as methylcellulose, sodium carboxymethylcellulose, and hydroxylpropylmethyl cellulose. Synthetic polymers such as carbomers, poloxamers, and polyvinyl alcohol are also used as suspending agents. The selection of buffers and preservatives for suspension formulation is similar to that for ophthalmic solutions in almost all aspects except that they must also be compatible with the flocculating systems.

In general, the manufacturing of ophthalmic suspensions is more complicated than conventional solutions and the key steps of the manufacturing process are depicted in Figure 2.1.

Continuous mixing is required during the filling process to assure homogeneity of the dosage form. Some of these steps may include aseptic handling of sterile materials. Sterilisation of the micronised active drug can be accomplished by dry heat, exposure to gamma irradiation or ethylene oxide or, in some cases, by steam sterilisation of the concentrated slurry.

An understanding of the interfacial properties, wetting, particle interaction, zeta potential, aggregation, sedimentation and rheological concepts is required for formulating an effective and elegant suspension. The critical problems that a formulator has to overcome during the development of a suspension are nonhomogeneity of the dosage form, settling, cake formation, aggregation of the suspended particles, resuspendability, effective preservation and ease of manufacture.

![Figure 2.1 Process of preparation of suspension](image-url)
2.3 Semisolids

Ointments consisting of a dispersion of a solid drug in a suitable vehicle base are the most commonly used semisolid preparations for ocular drug delivery. The use of semisolids in ocular drug delivery has helped in achieving improved drug efficacy and has added further dimensions to topical ocular drug delivery. Ointments are useful as drug carriers for improving bioavailability and for sustaining drug release. An attractive feature of ointments is their entrapment in the fornices, which thereby serve as a reservoir of the drug [14]. There is more flexibility in the choice of drug to be incorporated into an ointment base, as even drugs with low water solubility can be suitably delivered to the eye. The stability of drugs is sometimes even improved in ointments.

A drug added to an appropriate vehicle base is observed to provide an increase in the duration of action, due to various reasons. These include reduced dilution of the medicament by the tear film, reduced drainage due to high viscosity and prolonged contact time leading to sustained drug release. The desirable attributes for ointment formulations are: (a) they should not be irritating to the eye; (b) they should be uniform; (c) they should not cause excessive blurring of the vision and (d) they should be easy to manufacture. Ophthalmic ointments must be sterile, especially when used on injured eyes.

A typical manufacturing process for an ophthalmic ointment includes micronisation and sterilisation of the active agent by dry heat, ethylene oxide irradiation or gamma irradiation. All the materials used in the preparation of an ophthalmic ointment should be nonirritants to avoid discomfort to the patient and possible irritation. Semisolid ophthalmic vehicles frequently contain soft petrolatum, a bland absorption base, or a water soluble base. The water soluble base may be prepared with polyethylene glycols or with water soluble gums. If required, antimicrobial preservatives such as chlorobutanol or parabens are dissolved in a mixture of molten petrolatum and mineral oil and cooled to about 40 °C with continuous mixing to assure homogeneity. The sterilised and micronised active ingredient is then added aseptically to the warm sterilised petrolatum/mineral oil mixture with continuous mixing until the ointment is homogeneous. Presterilised ophthalmic tubes are then filled with the ointment.

The major disadvantage of ophthalmic ointments is that they cause blurred vision due to the refractive index difference between the tears and the nonaqueous nature of the ointment. The night time use of ointments is advised as it obviates the difficulty of blurred vision and prolongs the retention of the therapeutic agent compared with eye drops. However, dosage variability with ointments is greater than with solutions and sticking together of the eyelids results in poor patient compliance. More importantly, drug molecules may be entrapped within the ointment base or may not be released at the site of action due to a favourable partitioning towards the base. Thus, a true ‘sustaining effect’ is not achieved.
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Although topical application is by far the most common route of drug delivery to the eye, more often than not it fails to establish a therapeutic drug level for the desired length of time within the ocular tissues and fluids. Minimising the negative influence exerted by the ocular physiological processes on the precorneal residence time and enhancement of corneal drug penetration are the primary objectives of an optimised ocular drug delivery system. The development of ocular preparations has undergone notable changes over the course of many years and to date, pharmaceutical technologists have tried various formulation approaches to increase the bioavailability and duration of the therapeutic action of ocular drugs.

### 2.4 Summary and Conclusion

Conventional aqueous solutions topically applied to the eye have an inherent disadvantage in that most of the instilled drug is lost within first 15-30 seconds after instillation, due to reflex tearing and drainage via the nasolachrymal duct. The challenge faced by scientists involved in ophthalmic pharmaceutical research is to improve ocular drug bioavailability from less than 1-3% to at least 15-20%. Initial attempts to overcome the poor bioavailability problem involved the use of suspensions [15, 16] and ointments based on mixtures of white petrolatum and mineral oils [17, 18]. The use of suspensions as ophthalmic delivery systems relies on the assumption that particles may persist in the conjunctival sac. The efficiency of suspensions has shown high variability, which occurred as a result of inadequate dosing, probably due mainly to the lack of patient compliance in shaking the suspension adequately before administration [3]. Ointments ensure superior drug bioavailability by increasing the contact time with the eye, minimising the dilution by tears, and resisting nasolachrymal drainage. These vehicles have the major disadvantage of causing blurred vision and hence are recommended mainly for night time use or for the treatment of only the outside and edges of the eyelids [19]. The disadvantages associated with all these conventional ocular formulations led formulation scientists to investigate other novel formulation approaches in order to improve ocular drug delivery.

### References


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