

Ocular Insert: Dosage Form for Sustain Ophthalmic Drug Delivery

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Abstract

Except for skin, the eye is the most easily accessible site for topical administration of a medication. Traditional topical ophthalmic formulations (eye drops and ointments) have poor bioavailability because of rapid pre-corneal elimination, conjunctival absorption, solution drainage by gravity, induced lacrimation and normal tear turnover. This leads to frequent installations of concentrated medication to achieve a therapeutic effect. The typical “pulse-entry” type drug release observed with ocular aqueous solutions (eye drops), suspensions and ointments can be replaced by more controlled, sustained, and continuous drug delivery, using a controlled-release ocular drug delivery system. Ocular inserts are solid or semi-solid sterile preparations, of appropriate size and shape, designed to be inserted behind the eyelid or held on the eye and to deliver drugs for topical or systemic effect. These are polymeric systems into which the drug is incorporated as a solution or dispersion. They are better tolerated as to drainage and tear flow compared with other ophthalmic formulation and produce reliable drug release in the conjunctival cul-de-sac.

Key words: Eye, ocular inserts, films simulated tear fluid, cul-de-sac

Penyisipan Okular: Sediaan untuk Penghantaran Obat Mata Diperlambat

Abstrak

Mata adalah organ yang paling mudah dijangkau untuk pengobatan topikal selain kulit. Formulasi sediaan topikal tradisional untuk mata (tetes mata dan salep) memiliki ketersediaan hayati yang rendah karena cepat dieliminasi sebelum mencapai kornea, absorpsi konjungtiva, kekeringan cairan mata karena gravitasi, lakrimasi terinduksi, dan pergantian normal air mata. Hal ini mengarahkan pada penggunaan obat yang pekat secara berulang untuk menghasilkan efek terapi. Tipe obat *pulse-entry* seperti tetes mata, suspensi, dan salep dapat digantikan dengan penghantaran obat yang lebih terkontrol, diperlambat, dan berkelanjutan menggunakan sistem penghantaran obat okular yang pengeluarannya dikontrol. Sediaan penyisipan okular merupakan sediaan steril berbentuk solid dan semisolid, dengan ukuran dan bentuk yang sesuai, serta didesain untuk dapat disisipkan di belakang kelopak mata atau diletakkan di atas mata untuk menghantarkan efek obat secara topikal atau sistemik. Sediaan ini merupakan sistem polimer yang tidak larut atau terdispersi. Sediaan ini lebih baik dalam hal pengeringan dan aliran air mata dibandingkan formulasi sediaan mata yang lain dan menghasilkan pengeluaran obat yang reliabel pada konjungtiva kuldesak.

Kata kunci: Mata, penyisipan okular, simulasi cairan air mata *film*, kuldesak

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Introduction

The eye is unique organ from anatomical and physiological point of view, containing widely varied structures with independent physiological functions¹. Eye ailment can cause distress and angst in patients with the ultimate fear of loss of vision or even facial disfigurement.² A rapid expansion of new technologies in ocular drug delivery and new drug candidates, including biologics, to treat these challenging diseases in the anterior and posterior segments to the eye have recently emerged. These approaches are necessary because the eye has many unique barriers to drug delivery.³

Delivery of medication to the human eye is an integral part of medical treatment. The delivery of drug to the site of action has been practiced since ancient time, which successively advanced in a variety of ophthalmic dosage form.⁴ For the therapeutic treatment of most ocular problems, topical administration clearly seems the preferred route over systematic administration for obvious reasons^{5,6}:

1. The systemic toxicity of many ophthalmic drugs
2. The rapid onset of action and
3. The smaller dose required compared to the systemic route.

The topical ocular administration of drugs has two different purposes: to treat superficial eye diseases, such as infections (i.e. conjunctivitis, blepharitis, keratitis, sicca), and to provide intra-ocular treatment through the cornea for diseases such as glaucoma or uvetitis.⁷

At the present time, diseases of the eye are treated by applying ophthalmic drugs in liquid (eye drops) or ointment forms. These dosage forms are easy to install but suffer from the inherent drawbacks (Figure 1).⁸ The major deficiencies of these conventional dosage forms include poor ocular drug bioavailability, pulse drug entry after topical administration, systemic exposure because of nasolacrimal duct drainage and a lack of effective systems for

drug delivery to the posterior segment of ocular tissue.⁹ The physiological requirement to preserve visual activity poses significant problems in achieving sustained drug concentrations particularly associated with the need to provide a transparent formulation, reducing irritancy and avoid rapid clearance.¹⁰

Sustained and controlled delivery of drug to the ocular tissues continue to remain a major objective for formulation scientists and engineers in light of the emergence of more potent drugs and biological response modifications with limited biological half lives.¹¹ Various approaches that have been attempted to increase the bioavailability and the duration of therapeutic action of ocular drugs can be divided into two categories: the first is based on the use of drug delivery system, which provides the controlled and continuous delivery of ophthalmic drugs. The second involves maximizing corneal drug absorption and minimizing pre corneal drug loss. These systems can achieve therapeutic action with a smaller dose and a lesser systemic and ocular side effect.¹² These practical issues have stimulated the search for alternative methods for ocular drug delivery.¹³ Consequently, numerous novel ophthalmic drug delivery systems are developed to achieve a higher bioavailability of drugs. Among these formulations are in-situ gelling polymers, microspheres, nanoparticles, liposome and ocular insert.¹⁴ One of the new classes of drug delivery systems, polymeric film ocular drug delivery system/ ocular inserts, which are gaining worldwide accolade, serves as platform for the release of one or more active substances⁸. This review covers types, fabrication methods and evaluation of ocular inserts.

Ocular Insert

Solid inserts are introduced to the ophthalmic market 60 years ago. The earliest official record of a solid inserts are described in the 1948, British Pharmacopoeia. It is an atropine

containing gelatin wafer, Lamelli. The potential of solid inserts for sustained and controlled drug release was subsequently recognized and, in the 1979 & 1980s numerous systems were developed using various polymers and applying different drug release principles.^{9,15}

Ophthalmic inserts are sterile, solid or semi-solid preparations of suitable size and shape, dispensed to be inserted in the conjunctival sac

to produce an ocular effect. These inserts are placed in the lower fornix and less frequently, in the upper fornix or on the cornea. They generally consist of a reservoir of active substance embedded in a matrix or bounded by a rate controlling membrane. The active substance, which is more or less soluble in physiological fluid, is released over determined period of time at a relatively slow rate.^{8,16,17}

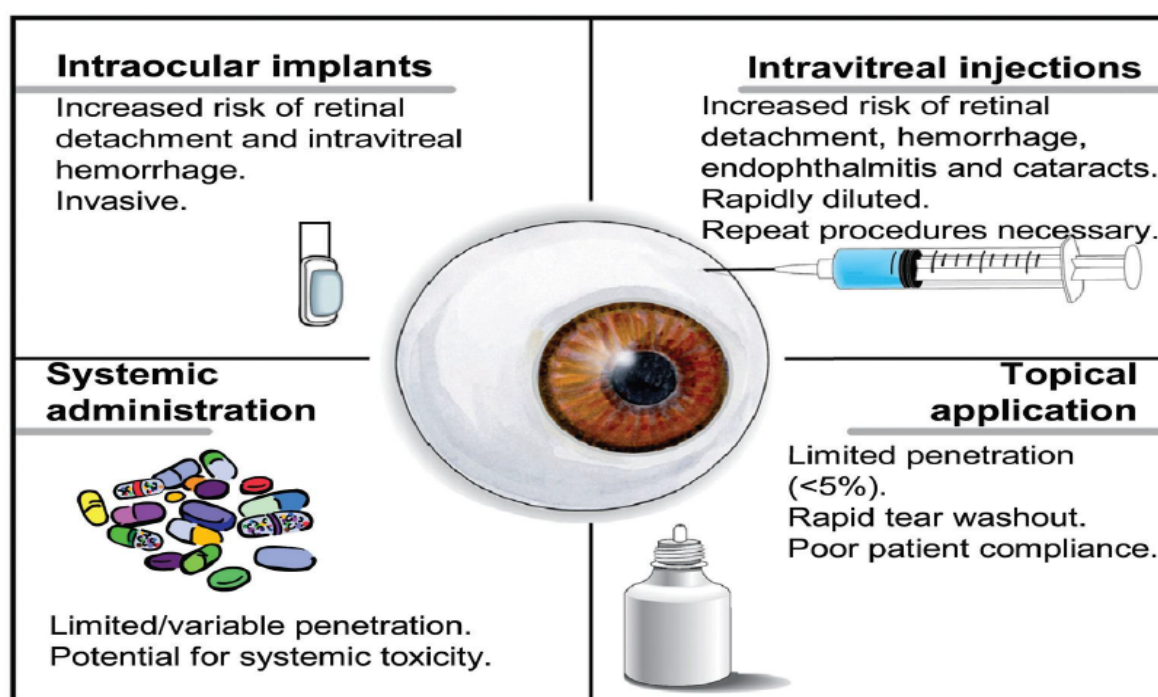


Figure1 Drawbacks of some ocular dosage form

Advantages and Disadvantages^{8,17,20}

In comparison with the traditional ophthalmic dosage form i.e. drops and ointments, the ocular inserts have some advantages such as

1. Increasing ocular contact time with respect to standard vehicles thus improving bioavailability.
2. Accurate dosing as the entire drug is retained at the absorption site.
3. Capacity to provide, in some cases, a constant rate of drug release.
4. Possibility to providing a prolong drug release and thus a better efficacy.
5. Reduction of systemic absorption thus reduces systemic side effects.
6. Reduction in frequency of administration, thus better patient compliance and a lower incidence of visual and systemic side effects.
7. Possibility of targeting internal ocular tissues through non-corneal conjunctival sclera penetration route.
8. Increased shelf life with respect to aque-

ous solution.

9. Possibility of incorporating various novel chemical/technological approaches such as prodrugs, mucoadhesives, penetration enhancers, microparticulates, salt acting as buffers etc.

Each type of insert represents a compromise between the desirable properties inherent to solid dosage form and negative constraints imposed by the structure and components of the insert itself, by fabrication costs, as well as by the physical/physiological constraints of the application site.

1. A capital disadvantage of ocular inserts resides in their solidity i.e. they are felt by the patients as a foreign body in the eye.
2. The occasional inadvertent loss during sleep or while rubbing the eyes.
3. Difficulty with self insertion.

Types of ocular inserts

A number of solid polymeric inserts have been developed as ocular drug delivery systems and are currently available in market or are in the later stages of development. They are better tolerated as to drainage and tear flow compared with other ophthalmic formulations and produce reliable drug release in the conjunctival cul-de-sac. Ocular inserts can be classified into two categories.²¹⁻²²

1. Degradable/Bioerodible/Biosoluble
2. Nondegradable

Degradable/Bioerodible/Biosoluble^{23,25}

Degradable/bioerodible/biosoluble ocular inserts are the ocular inserts for the continuous administration of a predetermined therapeutically effective dosage of drug to the eye over a prolonged period of time and comprise of drug formulation dispersed through a body of selected polymers which erode in the environment of the eye over a prolonged period of time to dispense the desired amount of drug.

These inserts are safe and convenient because they are biodegradable although the release process of the drug from these inserts is complicated under physiological conditions. The polymeric matrix will disappear from the eye by dissolution or erosion. These processes may coexist in some cases.²²

Various materials have been utilized in the development of degradable inserts including poly vinyl alcohol, hydroxyl propyl cellulose, poly vinyl pyrrolidone, hyaluronic acid²⁶ and polyethylene oxide²⁷. These polymers can form hydrogen bonds with water, therefore, when they come in contact with water, hydrate and eventually erodes as polymer dissolves.

Non Degradable/Bio insoluble^{28,31}

Non degradable inserts have also been developed with polymers related to soft contact lenses and ethylene vinyl alcohol copolymers. The matrix requires topical safety during application and removal from the eye after use. Drug release from the bio insoluble inserts may be more predictable than that from the biosoluble insert.²²

Such ocular inserts are fabricated of flexible polymeric materials that are biologically inert, non allergenic, and insoluble in tear fluid. Since the polymeric material is insoluble, in tear fluid it retains its integrity and remains intact during the course of therapy, acting as a reservoir to continuously release the drug to the eye and surrounding tissues at a rate which is not affected by dissolution or erosion of this polymeric material. On termination of the therapeutic program, the ocular insert is removed from the cul-de-sac. Exemplary materials for fabricating the ocular insert include hydrophobic polymers such as poly vinyl chloride, plasticized nylon, unplasticized soft nylon, plasticized polyethylene terephthalate and silicon rubber and hydrophilic polymers such as the hydrophilic hydrogels of esters of acrylic and methacrylic acid,

modified collagen, crosslinked hydrophilic polyether gels, cross linked PVA and cross linked partially hydrolyzed polyvinyl acetate.

Fabrication of Ocular InsertnSolvent Casting Technique/Mercury Substrate Method^{32,33}

The required amount of polymer is dissolved in appropriate solvent, with the help of magnetic stirrer to form the reservoir. Plasticizer and drug are incorporated into above solution under stirring conditions to form homogenous solution. After complete mixing, the drug reservoir solution is kept overnight to remove any entrapped air bubbles. The polymeric solution is then poured over a glass ring or mercury substrate and covered with an inverted funnel to allow slow and uniform evaporation at temperature around 50°C in a oven for 48 hours. The dried film so obtained are carefully removed and cut into appropriate size using a sterile stainless steel borer or sharp edged die.

Moulding technique³⁴

A glass mould of appropriate size (10 cm. length, 5 cm. width and 1.5 cm. height with a total surface area of 50 cm²) is fabricated for formulation of inserts. A drug-reservoir polymer solution is made (as per solvent casting method) and then placed under vacuum to remove the air bubbles. The polymer drug solution is then poured into prelubricated glass mould and kept for drying in a hot air oven at 50°C till complete drying. The film is cut into appropriate size with stainless steel borer.

Compression^{35,37}

Polymers, active ingredients and plasticizers are mixed properly. The polymer mixture are then compressed by a hydraulic press or using tablet punching machine at the highest possible force (around 1000 kg). The production method is based on direct compression.

Melt Extrusion Technique^{17, 38}

Melt extrusion is a technique in which during extrusion, a polymer melt is pumped through a shaping die and formed into a profile. This profile can be a plate, a film, a tube, or having any shape of its cross section. In film extrusion, the polymer melt is extruded through a long slit die onto highly polished cooled rolls which form and wind the furnished sheet. This is known as cast film. The calculated dose of drug and the polymer are sieved through sieve no 60#, weighed and blended geometrically. The plasticizer is added and blended. The blend is then charged to the barrel of melt flow rate apparatus and extruded. The extrude is cut into appropriate size and packed.

Evaluation of Ocular Insert

Thickness of film^{39, 42}

Thickness of the film is an important factor while considering drug release from ocular delivery systems. If thickness varies from one film to another, the drug release from the film will also vary. So it is must to keep the thickness of the film uniform to get reproducible results. Thickness of film can be measured by using dial calipers, micrometers or dead weight thickness gauge at different point and then calculating the mean value.

Weight variation or uniformity of weight^{40, 43}

Variation of the films can lead to difference in drug content and release of the drug from the films. The weight variation test is carried out using digital balance or an electronic balance. 3-5 inserts from each batch are randomly selected, weighted individually. The average weight and standard deviations of weight variation is calculated.

Drug Content Uniformity⁴⁴⁻⁴⁶

Uniformity of the drug contents is determined

by assaying the inserts. The optimized ocular insert is powdered into a glass pastal & mortar and dissolved in 25 ml. isotonic phosphate buffer of pH 7.4 with occasional stirring. The resultant solution is filtered through a G-2 glass filter. From this, sample is taken, diluted suitably and analyzed spectrophotometrically.

Surface pH determination

1. Surface pH of the inserts is determined by allowing them to swell by placing 2 drops of double distilled water over it or by placing them in a closed petridish containing 0.1 ml. of double distilled water for 30 minutes at room temp. After this the swollen devices are removed and placed on the pH paper to determine the surface pH. After one minute the colour developed is compared with the standard colour scale.^{44, 45, 47}
2. Inserts are left to swell for 5 hours on agar plate prepared by dissolving 2% (w/v) agar in warm stimulated tear fluid of pH 7.2 under stirring and then pouring the solution into petri dish till gelling at room temp. The surface pH is measured by means of a pH paper placed on the surface of swollen patch.⁴²

Folding Endurance Value^{39, 42, 43, 45, 48}

The folding endurance is expressed as the number of folds or number of times the inserts is folded at the same place, either to break the specimen or to develop visible cracks. This test is important to check the ability of the sample to withstand folding. This also gives an indication of brittleness. The specimen is folded in the center, between the fingers and the thumb and then opened. This is termed as one folding. The process is repeated till the insert showed breakage or cracks in center of inserts. The total folding operations are named as folding endurance value.

Percentage Moisture Absorption

The percentage moisture absorption test is carried out to check physical stability or integrity of ocular inserts. Ocular inserts are weighed and placed in a desiccators containing 100 ml. of saturated solution of aluminium chloride (79.5% humidity)^{41, 43, 48-49} or ammonium chloride (79 % humidity at 30°C).⁵⁰ After three days, the ocular inserts are taken out and re-weighed. The percentage moisture absorption is calculated using the formula.

$$\% \text{ Moisture Absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage Moisture Loss^{39, 43, 48, 49, 50}

Percentage moisture loss is carried out to check integrity of the film at dry condition. Ocular inserts are weighed and kept in the dessicator containing anhydrous CaCl₂. After three days, the inserts are taken out and reweighed. The % moisture loss is calculated using the formula:

$$\% \text{ Moisture Loss} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Determination of water uptake and swelling behavior/ Swelling Index^{14, 42, 43, 51}

Swelling of the polymer depends on the concentration of the polymer, ionic strength and the presence of water. Water uptake is determined gravimetrically. Initial weight of the ocular inserts is taken. Inserts is placed on a filter. The lower side of the filter is immersed in a beaker containing simulated lacrimal fluid or inserts can be placed directly on agar gel plate. The inserts are incubated at 32°C, the eye surface temperature. The beaker is closed with paraffin to prevent evaporation during the

experiment. Inserts are removed at predetermined time periods, surface water is removed with the help of filter paper and inserts are re-weighted using an analytical balance. The % of swelling or swelling index is calculated by the following equation.

$$\% \text{ Swelling Index} = \frac{W_t - W_0}{W_0} \times 100$$

Where W_t is the weight of swollen insert after time t and W_0 is the initial weight of insert. The size changes of the inserts due to swelling are investigated macroscopically.

$$\text{MVT Rate} = \frac{W L}{S}$$

Where W = Gm. of water transmitted
 L = Thickness of film
 S = Exposed surface area of film

Mechanical Strength^{33, 42, 52}

Ocular inserts with good tensile strength and percent elongation would resist tearing due to stress generated by blinking action of eye. Percentage of elongation at break and tensile strength of film are measured using a pulley based tensile strength apparatus. The apparatus consisted of a base plate with a pulley aligned on it. The film is cut into strips (around 4×1 cm). The film is fixed in insert holder at one end of the base plate and another end is kept with the help of forceps having triangular end to keep the film straight during stretching. A thread is tied to the triangular end and passed over the pulley to which a small pan is attached to hold weights. A small pointer is attached to the tread that travels on the graph paper affixed on the base plate. The weights are gradually added to the pan till the film is broken. The weight necessary to break the film is noted as break force and the simultaneously distance travelled by the pointer on the graph paper indicated the elongation at break.

$$\text{Tensile Strength (g/mm}^2\text{)} = \frac{\text{Break Force (g)}}{\text{Cross sectional area of the sample}}$$

$$\text{Tensile Strength (g/mm}^2\text{)} = \text{Break Force (g)} \times \frac{1 + \Delta L/L}{a.b}$$

Where ΔL = elongation at break

L = length of the film

a = width of film

b = thickness of film

Break force = Weight required to break the film

$$\% \text{ elongation at break} = \frac{(l_b - l_0)}{l_0} \times 100$$

l_b = length of film at break when stress is applied

Ocular Irritation Test^{40, 45, 47, 53, 54}

Ocular irritation studies are performed according to the Draize Irritancy test. The test has been standardized at the international level, e.g. using the OECD guidelines and test guideline 405. The OECD guideline for eye irritancy test is currently the most valuable and reliable method for evaluating hazard or safety of a substance introduced into or around the eye. The ocular irritancy potential of a substance is evaluated by observing them for any redness, inflammation or increased tear production (Table I). The observation based on scoring approach (Table 2) established the safety of ocular insert in the eye. Testing is carried out on adult albino rabbits weighting about 2.5 to 3.5 kg of either sex. All rabbits are maintained under 12 h light and dark cycles and are fed with green vegetables throughout the course of study. Food and water is allowed ad libitum. Twelve rabbits are used for testing the eye irritation potential of the ocular insert.

The sterile formulation is placed into the cul-de-sac of the rabbit while other eye served as

a control. The rabbits are observed periodically for redness swelling and watering of the eyes of them.

Table 1 Draize irritancy test for ocular safety

Ocular Tissue	Scoring Scale	Calculation	Total
Cornea: Opacity (O)	0,1,2,3,4	$O \times A \times 5$	80
Area involved (A)	0,1,2,3,4		
Iris: Values for congestion and hemorrhage (I)	0,1,2	$y I \times 5$	10
y Conjunctiva: Redness (R)	0,1,2,3	$y (R+C+D) \times 2$	20
Chemosis (C)	0,1,2,3,4		
Discharge (D)	0,1,2,3		
Total Max. 110			110

Note: Score of 0 is normal, 3 and 4 is severe in case of O, R, C and D. Score of 0 is none, 1,2,3,4 is the extent of cornea covered for A. Score of 0 is normal and 2 is severe in case of I.

Table 2 Safety evaluation chart

Score	Rating
0.0 – 0.5	Non Irritating
0.5 – 2.5	Practically Non Irrigating
1.5– 15.0	Minimally Irritating
15.0 – 25.0	Mildly Irritating
25.0 – 50.0	Moderately Irritating
50.0 – 80.0	Severely Irritating
80.0 – 110.0	Extremely Irritating

Mucoadhesive Strength/Bioadhesive Strength^{27, 34, 42}

Mucoadhesive strength is calculated by measuring the work required to detach the unit surface of sample from a mucous membrane.

Mucoadhesive strength is measured on a modified physical balance and the freshly excised conjunctiva membrane or the mucous membrane from the intestine of goat is used as model mucous membrane. Membrane is tied to open mouth of a glass beaker filled with STF (pH 7.2; 32 °C). Separately, insert is adhered to the lower side of a rubber stopper, which is attached to lever of a physical balance. The mass, put on other limb of balance,

which is required to detach the patch from the conjunctival surface, is a measure of Bioadhesive strength. Force of adhesion is calculated by given formula Force of adhesion (N) = (Bioadhesive Strength x 9.81) /1000

In vitro drug release study

1. Bi-chamber donor-receiver compartment model^{54, 55}

In vitro release studies are carried out using a bi-chamber donor-receiver compartment model using commercial semi permeable membrane. The cellophane membrane, presoaked overnight in the freshly prepared dissolution medium (STF, pH 7.2) and is tied to one end of an open cylinder (open

at both the sides), which acts as the donor compartment. The semi permeable membrane is used to mimic in vivo conditions, like a corneal epithelial barrier. The ocular insert is placed inside the donor compartment. In order to simulate the tear volume, 0.7 ml. of water for injection is placed in donor compartment and maintained at the same level throughout the study. The entire surface of the membrane is in contact with the reservoir compartment containing 25 ml of pH 7.4 phosphate buffer by suspending the donor compartment into reservoir with the help of a clamping stand. The dissolution medium is stirred continuously at a low speed using magnetic stirrer. The aliquots of defined quantity of sample is withdrawn from receptor compartment at periodic intervals and replaced with equal volume of phosphate buffer pH 7.4. The samples are analyzed spectrophotometrically.

2. Open Flow Through Apparatus^{56, 57}
The open flow through apparatus mimics the continuous flow of tears to a certain extent but the constant blinking action of the eye is not attempted to be simulated. The apparatus consisted of a 2 ml. glass tube open at both ends used as an in vitro diffusion cell. Two fluted glass adaptors are fused at both ends so that one formed inlet and the other fluted end used to withdraw samples. The inlet of this tube is connected to a reservoir containing isotonic phosphate buffer saline (IPBS) pH 7.4, with the help of PVC flexible tubes which had 2 ml. of buffers. The rate of flow of buffer is controlled with a valve. The head of reservoir kept constant. The setup is validated. IPBS pH 7.4 is put into the reservoir. A small volume of fluid is allowed to drain away, so as to remove any entrapped air bubbles, in the cell. An ocular insert is stuck on to a thin, small, circular, Teflon disk, so that only one surface is exposed to

the dissolution medium. The disk is steadily inserted into the cell containing 2 ml. of fluid. The temperature of fluid is kept at $37\pm 1^\circ\text{C}$. At regular intervals diffusion fluid is taken to analyze the drug content using spectrophotometer.

3. The inserts are placed in a beaker containing defined quantity of phosphate buffer pH 7.4 kept at $37\pm 1^\circ\text{C}$, under control stirring. At various intervals sample are withdrawn and analyzed spectrophotometrically.^{43,46}

In vivo Release Study^{22, 58}

Approval of the use of animals in the study is obtained from local animal ethical committee. Adult Newzeland Albino rabbits of either sex are used to study the in vivo release. Each rabbits are kept in good hygienic condition in order to avoid vulnerability of any disease including ophthalmic type. The rabbits are housed singly in restraining boxes during the experiment and allowed feed with standard diet and water ad libitum. Free legs and eye movements are allowed.

The inserts are sterilized before in vivo study. Selected ocular inserts are placed in the lower cul-de-sac of each rabbit while the other eye served as a control. At periodic intervals the inserts are taken out carefully from and analyzed for the remaining drug content as mentioned in drug content uniformity. The drug remaining is subtracted from the initial drug content of the drug, which gave the amount of drug released in the rabbit eye.

Observation for any fall out of the inserts is also recorded throughout the experiment. After one week of wash period the experiment is repeated for two times as before.

Sterility study^{33, 41, 51}

It is done for detecting the presence of viable forms of microorganisms in the preparation. The working conditions should be

monitored regularly by taking the samples of air and surface of working areas and there should not be any cross contamination.

The sterility test is carried out using direct inoculation method as described in Indian Pharmacopoeia. The test is based on the principle that if the nutrient media is provided to the microorganisms and they are kept in favorable conditions of temperature, the microorganisms will grow and their pre-sence is indicated by the turbidity of medium.

A sterilized ocular insert is placed in a culture tube containing ten ml. of sterile media. The mouth of the tube is tightly closed and incubated in (a) Fluid Thioglycollate medium / Alternate Thioglycollate medium at 30 °C to 35°C and (b) Soyabean casein digest medium at 20° to 25°C for not less than seven days. The tubes are examined visually for signs of any microbial growth during the incubation period. Positive and negative controls are also employed in order to support the test.

Stability test^{39, 49, 57}

The stability studies are conducted according to ICH guidelines by storing ocular inserts at $40 \pm 0.5^\circ\text{C}$ and $75 \pm 5\%$ RH for 6 months. Samples are withdrawn at 0, 30, 60, 90 and 180 days and evaluated for physical parameters, in vitro release, sterility and drug content. The degradation rate constant is determined from the plot of the percentage drug remained vs time in days. $\text{Slope} = -K / 2.303$

Where K is degradation rate constant.

Conclusions

The physiological constraints imposed by the protective mechanisms of the eye leads to low absorption of drugs and a short duration of therapeutic effect on ocular drug delivery. A basic concept in ophthalmic research and development is that the therapeutic efficacy of an ophthalmic drug can be greatly improved by

prolonging its contact with the corneal surface. Ophthalmic inserts offer several advantages over conventional dosage forms, like increased ocular residence, possibility of releasing drugs at a slow and constant rate, accurate dosing, exclusion of preservatives, increase shelf life and reduced systemic absorption.

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