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(REVIEW ARTICLE)

Ocular inserts: Novel approach for drug delivery into eyes

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Abstract

As an isolated organ, it is difficult to study eye from a drug delivery point of view. Ophthalmic drug delivery is extremely interesting and highly challenging attempt. In recent scenario, most eye-diseases are treated with topical application of eye-drops. But these conventional eye-drops have two major problems. One is it needs frequent administration at every 4 hours or 1 hour if the infection is severe and another is formation of crystalline deposits on cornea due to its pH-dependent solubility which is very low. In order to provide the solution of above problems many novel formulations have been developed. Ocular insert is one of them. Ocular inserts are defined as sterile, thin, multilayered, drug-impregnated, solid or semisolid consistency devices placed into the cul-de-sac or conjuctival sac, whose size and shape are especially designed for ophthalmic application. The review study emphasizes on advantages of ocular inserts over conventional dosage forms. The study includes physiology of eye, various preparation and evaluation methods of ocular inserts.

Keywords: Eye; Ocular drug delivery; Ocular inserts; Cul-de-sac

1. Introduction

1.1. Ocular drug delivery system

Ocular drug delivery system requires the need to study anatomy, physiology and biochemistry of eye in order to overcome the challenge making to attack the protective barrier of eye without causing permanent tissue damage. Research till now in ocular drug delivery system focused towards several drug delivery technologies developing the system which will not only prolong the contact time of vehicle at the ocular surface but also slow down the elimination process of drug. In this field ocular inserts would be the most innovative step [1].

1.2. Ocular anatomy and physiology

The eye has been characterized as a complex structure and highly resistant to foreign substances including drugs. There exist several parts resemble the human eye as a “camera”. The anterior and posterior segment of the eye is the two main different sections having anatomical and physiological function. Thus application of ocular preparation also differs; as conventional topical formulations are mainly applied to anterior portion and most of applied dose is lost due to the defensive mechanism of eye. Thus there is a need of concerned efforts to direct the formulation and increase the retention time on eye surface for better therapeutic effect and low systemic / local effect [2].

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1.3. Structure of eye [3]

Following section describes the eye parts along with the problems arising with conventional ocular preparation.

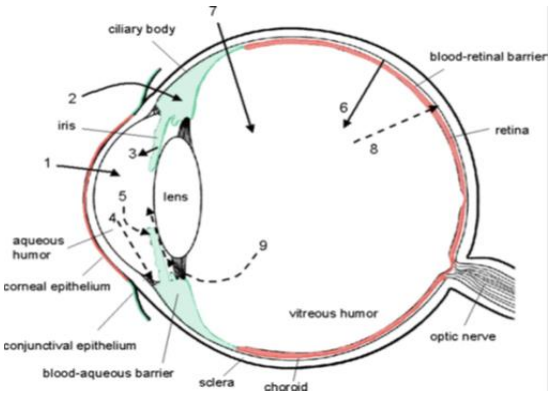

Figure 1 Structure of eye

Sclera is white outer protective coat i.e. white of the eye. Cornea is the transparent, curved structure at the front of the eye and has poor penetration of drugs. Iris is coloured part of the eye. The pupil is the black part of eye in the middle of iris. The lenses are transparent disc immediately behind iris and pupil. Aqueous humour is the transparent fluid that circulates behind the cornea and in front of the lenses. Vitreous is the material (like transparent jelly) that fills the eyeball between lens and retina. Retina is light sensitive layer of millions of nerve cells that line the back of the eye ball. Choroid is a large network of blood vessels that transport oxygen and other nutrients to the retinal pigment cells [3].

Systemic administration or intravitreal injection and implant are preferred via retina, vitreous humour and choroid. The conjuctivial tissue/ choroid tissue are sensitive towards penetration enhancers leading to maximize drug effects but cause high degree of risk, also there is restriction due to strong blood-ocular tissue barrier require larger dose for therapy. Thus there is a need of controlled drug delivery system to prolong the pre-corneal resistance time along with a therapeutic effect. There exist various diseased conditions in which the medication dosing frequency is 4-5 times in a day i.e. a tedious task. Thus preparation of such delivery systems in which the drug release is sustained for up to 8-12 hours a day. This reduces the drug frequency.

2. Types of ophthalmic dosage forms

There are numerous ocular dosage forms classified as follows:

2.1. Ophthalmic solutions

Solution is one of the most frequent dosage form used in the eye. The drug in the solution remains active as it enters in the eye surface after passing through cornea or conjunctiva. The main disadvantage of solution is their less retention time in the eye, reduced bioavailability as 75% of solution is removed through nasolacrimal fluid and unsteadiness of the drug and a need of preservatives. The demerits of eye can be shorted reduced by using viscosity enhancing agent in the solution as it increases the retention time of drug in the eye or changing the pH of the solution [4].

2.2. Ophthalmic suspensions

Suspensions may be defined as a dosage form containing small divided insoluble drug particle dispersed in aqueous vehicle having suspending and dispersing agent. The retention time of the suspension is longer in comparision of solution because of the ability of the particle to remain in the cul-de sac. The dissolution rate of particles of suspension is inversely proportional to the particle size. Therefore for suspension, a suitable particle size should be selected for the delivery of drug into eye for better dissolution which would be less than 10μm [5].

2.3. Sol-gel system

It is a newer concept of producing a gel from solutions by increasing the amount of viscosity enhancing agent in the solution. As a result, viscosity of drug solution increases which result in gels leads to increased contact time and bioavailability and less drainage from cornea. Many concepts have been discovered for the formation of in-situ gels

these systems show there activation by change in pH, temperature or by ion activation. The viscous solution or gels may result in increased contact time in the eye surface for the absorption of drug but it can cause irritation to eye [5].

2.4. Ophthalmic ointments

Ophthalmic ointments are semi solid dosage form containing mineral oil and white petroleum jelly as the base whose concentration varies according to the consistency needed for the ointment and the melting temperature. Drug loading in ointments is greater than in case of solution .Due to high consistency and viscosity of ointments, it can affect the vision of eye which is the min disadvantage of ointments. So its application only limited to the nights before sleeping. Only moisture sensitive drug can be delivered by base ingredients due to its anhydrous nature. Ointments are mostly preferred by pediatric patients. The main advantages of ophthalmic ointments are greater contact time and increased absorption of total drug. The relationship that describes the presence of small particle of drug dispersed in ointment base was described by Highuchi model. According to it, the amount drug released per unit time is a function of concentration, solubility of drug in base, diffusivity of the base [5].

2.5. Ophthalmic emulsions

Ophthalmic dosage forms have advantage of delivery the poorly water soluble drug. The emulsion consist of two phase oil phase or non-aqueous phase in which the drug is dissolved or aqueous phase which are made miscible using emulsifying agent. Emulsion is of two types-o/w type or w/o type, out of which w/o type in which water in the external phase is less irritating to the eye can be bearable by patient than o/w type emulsion [6].

3. Ocular inserts [7]

Ophthalmic inserts are sterile preparations, having a solid or semisolid uniformity and whose size and shape are especially designed in such a way that they should be suitable for ocular uses. Composition of ocuserts includes polymeric support in which drug(s), incorporated in form of dispersion or a solution. For topical or systemic therapy in eye ocuserts can be used. The main purpose of the use of ophthalmic inserts is to enhance the retention time of active form of drug between in eye to ensure a sustained release suited.

In comparison with other liquid formulation the ocuserts have numerous benefits Because of the prolonged retention time of the device and a controlled release, an efficient concentration of drug in the eye can achieved for extended time. Dosing frequency can also be reduced and risk of systemic adverse effect is decreased.

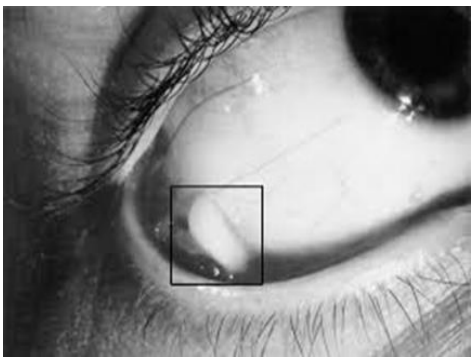

Figure 2 Ocular insert

3.1. Advantages [8]

- Reduced number of dose administration thus better patient compliance.
- Increased contact time and thus improved bioavailability.
- Systemic side effects can be decreased thus reduction in adverse effect.
- Accurate dosing (contrary to eye drops that can be improperly instilled by the patient and are partially lost after administration, each insert can be made to contain a precise dose which is fully retained at the administration site).
- Possibility of targeting internal ocular tissues through non-corneal (conjunctival sclera) routes.
- Prohibiting the use of preservatives, thus reducing the risk of sensitivity reactions.
- Possibility of incorporating various novel chemical/technological approaches.

4. Classification of ophthalmic inserts

Depending on solubility ophthalmic inserts are classified as following:

4.1. Insoluble inserts

This category of inserts includes diffusion and osmotic systems in which drug reservoir is placed between the rate controlling polymers for supplying the drug in a controlled manner. In the reservoir system the drug is dispersed or dissolved in a polymer in form of liquid, a gel, a colloid, a semisolid or a solid matrix.

The polymer which is used as a carrier may be hydrophobic, hydrophilic, organic, inorganic, naturally occurring or synthetic material in nature [9, 10].

4.2. Soluble inserts

This type of inserts belongs to oldest class of ocular inserts. The main advantage of these inserts is that as they are completely soluble so there is no need of removal from the site of application. The therapeutic agents are preferably absorbed by soaking the insert in a solution containing the drug, drying and re-hydrating it before use on the eye. The amount of drug loaded will depend upon the amount of binding agent, upon the concentration of the drug solution into which the composite is soaked, as well as the duration of soaking [10].

4.3. Bioerodible inserts

The bioerodible inserts consist of homogeneous dispersion of a drug with or without of coating of hydrophobic coating which is considerably not permeable to the drug .As the name indicate bioerodible polymers are used in the formulation of this inserts. The bioerodible materials which are suitable for ophthalmic use are the poly (orthoesters) and poly (orthocarbonates) etc The drug release of these system depends on the contact of the device from tear fluid showing a apparently bioerosion of the matrix[10].

5. Mechanism of drug release

The mechanism of controlled drug release into the eye is as follows:

5.1. Diffusion

In this mechanism, the release of drug through the membrane into the tear fluid occur continuously in a controlled manner In case the insert is made up of non-erodible solid body with pores and the drug is dispersed, the release of drug takes place through pores following diffusion. Controlled release can also be achieved by optimum dissolution of solid dispersed form of drug within the matrix, result of diffusion of aqueous solution. In soluble systems as the polymer swells, true dissolution takes place. In swelling-controlled devices, the drug in active form is dispersed in a glassy polymer homogeneously. Diffusion does not takes place via dry matrix because the glassy polymer are impermeable to drug.

When the device is inserted into the eye, water from the tear fluid starts penetrating the matrix, then swelling of polymer with chain relaxation begins, then drug diffusion take place. The matrix dissolution which follows the swelling process, depends on of structure of polymer as linear and amorphous form of polymers dissolve much faster as compared to cross-linked or partially crystalline polymer [11].

5.2. Osmosis

In the Osmosis mechanism, the insert consists a slating elastic membrane that is impermeable separating the inner part of the insert into two compartments, in the first compartment there is a the impermeable elastic membrane, and the semi-permeable membrane on the other hand second compartment consists of an impermeable material and the elastic membrane. For drug release there is gap in the impermeable section of the insert.

In the first compartment there is a solute which cannot cross the semi-permeable membrane and the second compartment supplies a reservoir for the drug which again is in liquid or gel form. When the insert comes into the contact with aqueous environment of the eye, water diffuses into the first compartment and enlarges the elastic membrane to open out the first compartment and contract the second compartment so that the drug is forced through the drug release [11].

5.3. Bioerosion

In the Bioerosion mechanism, the design of the body of the insert is composed from a bioerodible polymer matrix in which the drug is dissolved. Controlled/ sustained release of the drug is achieved by bioerosion of the matrix when the device comes into the contact with aqueous eye environment [11].

6. Formulation method of ocuserts [12]

6.1. Solvent casting method

In this method no. of batches are prepared using different proportion. The polymer is dissolved in suitable solvent. Into this solution plasticizer is added following continuous stirring the accurately weighed amount of drug is added to above solution and a uniform dispersion is obtained. When the proper blend is formed the solution is casted into the petridish using inverted funnel to allow slow and uniform evaporation at room temperature until the film is dried. The dried films thus obtained the film is cut into proper size and shape using cork borer The ocuserts are prepared and stored in air tight container.

6.2. Glass substrate technique

In this method the polymer is soaked in 1%v/v Acetic acid solution for 24hrs, to get a clear solution. The solution is filtered. Required amount of drug is added and vortexed for 15minutes to dissolve the complex in polymer solution. Plasticizer is added to the above solution. The viscous solution is obtained and kept aside for 30 minutes until air bubbles are removed The rate controlling films are formed. The films are casted by discharging solution into the centre of levelled glass mould and allowing it to dry at room temperature for 24 hrs. The dried films are cut to form ocusert in definite shape and size Then, the matrix is sandwiched between the rate controlling membranes using gum which is non-toxic, non-irritating, and water insoluble .They are wrapped in aluminium foil separately and stored in a desiccator.

6.3. Melt extrusion technique

Drug and the polymer are passed through sieve having mesh size of 60#, weighed and blended. In this mixture plasticizer is added. The blend is then discharged to the container of Melt flow rate apparatus and extruded.The extrudate was cut into appropriate size and packed in polyethylene lined Aluminium foil, heat sealed and sterilized by gamma radiation.

7. Evaluation parameters of ocuserts

7.1. Uniformity of weight

All the prepared film are weighed separately and weight of each film is noted. Then the average weight of film is calculated. The standard deviation is calculated from the mean value [13].

7.2. Percentage moisture absorption

For the calculation of percentage moisture absorption of the ocular inserts, the inserts are weighed and placed in desiccators containing 100 ml of saturated solution of aluminum chloride. Ocular inserts are reweighed after three days. The formula for calculating Percentage moisture absorption is:

Percentage moisture absorption = Final weight – Initial weight/ Initial weight × 100 [14].

7.3. Thickness

Thickness of each film is measured using Vernier Caliper and the average thickness of all the films is calculated.

7.4. Swelling index

Small amount of film is cut and weighed initially and then it is soaked in pH 7.4 tear fluid for 1 hour. After 1 hour, film is reweighed. Swelling index is calculated by following formula [15, 16].

Swelling index = initial weight/ final weight *100

7.5. Drug content uniformity

Small amount of inserts is cut and dipped in 7 ml of tear fluid. Then it is taken in centrifuge tube and centrifuged for 15 min. Then it is analyzed in UV spectrometry and concentration of drug is calculated using standard plot [15, 16].

7.6. Surface pH

Insert is placed in closed Petri plate in distilled water for half hour. After this the swelling of insert occurred. Swollen insert is then placed in digital pH meter to determine surface pH [15, 16].

7.7. Folding endurance

Film is started to fold from one side and folded many times until tearing of film is done. The number of fold occurred in film is its folding endurance till its breakage. The folding endurance of all the film is measured [16, 17].

7.8. *In vitro* diffusion studies

An *In vitro* diffusion study of ocuserts is done by using Franz diffusion cell. It is an instrument used to study the permeability study of drug. It consist of two compartment, one is donor compartment in which dosage form i.e. ocusert is added and another is receptor compartment which is filled with 7.4 tear fluid to simulated the tear fluid in eye. Both compartments are separated by membrane which may be semi permeable dialysis membrane or egg membrane. The instrument is started, RPM and temperature is adjusted. Ocusert is placed in donor compartment and tear fluid in receptor compartment. 1ml sample is withdrawn after fixed time interval and after making suitable dilution sample is analyzed in UV spectrophotometer. Sample is withdrawn until a constant absorbance is not obtained. Drug release is calculated [17, 18].

8. Conclusion

It's evident that drug delivery to the eye shows significant and important complication. Conventional dosage form needs frequent administration at every 4 hours and formation of crystalline deposits on cornea due to its pH-dependent solubility which is very low. Ocular inserts are developed to accommodate the increasing number of patients requiring treatment with minimized side effects. Ocuserts reduced number of dose administration thus improving better patient compliance. It increases contact time and thus improve bioavailability. Systemic side effects can be decreased, hence reducing in adverse effect. The use of preservatives is prohibited thus reducing the risk of sensitivity reactions. Ocular inserts are prepared with different method and can be evaluated with different parameters. Ocuserts are novel approaches in the era of ocular drug delivery compliance with ethical standards.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors declare that they have no conflict of interest.

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