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Review Article

# Design Expert Software Empowering Ocular Drug Delivery: Learning From Past Successes With Ocular Inserts

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## A B S T R A C T

The primary objective of this review is to explore the techniques adopted that can slow down the excretion of drugs from the ocular surface and prolong the contact time of the medication with the target tissues. Ocular inserts have emerged as a promising approach in this regard and can be broadly categorised into three types: soluble, insoluble, and biodegradable ocular inserts. In the field of ophthalmic formulations, conventional dosage forms are widely used, accounting for approximately 90% of the products available in the market. However, one of the main challenges faced with conventional formulations is the rapid loss of medication from the cornea, leading to reduced bioavailability and efficacy of ocular medications. To overcome this challenge and improve the delivery of ocular medications, significant efforts have been focused on the development of novel drug delivery systems specifically designed for ophthalmic administration. Recent studies in this area have explored the combination of different drug delivery technologies to achieve enhanced therapeutic outcomes. Overall, the development of ocular inserts represents a significant advancement in the treatment of various eye diseases. These inserts offer the potential to improve drug bioavailability, prolong therapeutic effects, and enhance patient compliance by reducing the frequency of administration. The work summarises that further research and development efforts are needed in this field to refine these technologies and optimise their effectiveness in ocular drug delivery.

**Keywords:** Bioavailability, Innovative Drug Delivery, Ocular Insert, Polymers

## Introduction

Ophthalmic inserts are specialised sterile preparations designed for use in the eyes. They are typically solid or semisolid in consistency and are shaped and sized in a manner that allows for easy insertion into the eye. The inserts are composed of a polymeric support material that may contain one or more drugs, either in the form of a dispersion or solution.

The primary purpose of ophthalmic inserts is to provide a sustained release of the drug(s) over an extended period of time. By doing so, they aim to prolong the duration that the active form of the drug remains in contact with the eye tissues. This sustained release effect is crucial for achieving therapeutic efficacy and reducing the frequency of administration required.

Ophthalmic inserts can be utilised for both topical and systemic therapy. In topical applications, the inserts are placed directly onto the ocular surface, allowing for localised drug delivery to the eye. Systemic therapy refers to the delivery of drugs through the eye to reach the systemic circulation and exert effects on other parts of the body.

The choice of polymeric materials for the insert's support plays a significant role in determining the release profile of the drug(s). The polymer matrix can be designed to control the release rate, allowing for a gradual and sustained release of the drug(s) over time. This sustained release feature is particularly advantageous in the treatment of chronic ocular conditions, as it can help maintain therapeutic drug levels within the eye and improve patient compliance.

Overall, ophthalmic inserts serve as an effective drug delivery system for ophthalmic applications. They offer the benefits of extended drug release, improved bioavailability, and reduced dosing frequency. Ongoing research and development in this area continue to explore innovative formulations and technologies to optimise the performance of ophthalmic inserts for enhanced therapeutic outcomes in ocular treatments.[1]

Ocular inserts, commonly referred to as "Ocuserts," are sterile preparations designed to prolong the residence time of drugs in the eye while minimising their impact on nasolacrimal drainage. These inserts utilise a diffusion-controlled release mechanism, where a central reservoir contains the drug and is surrounded by a specially designed micro-porous membrane. This membrane allows for controlled diffusion of the drug from the reservoir at a predetermined rate. Ocuserts are available in various forms depending on their content and intended use. They can be solid, semi-solid, or gel-like in consistency. The specific design and composition of the insert are tailored to achieve the desired drug release profile. One of the significant advantages of Ocuserts over traditional liquid formulations is the ability to maintain an effective drug concentration in the eye for an extended period. The longer retention time of the insert and controlled release mechanism contributes to this advantage. As a result, the frequency of dosing can be reduced, leading to improved patient convenience and compliance.[2] Furthermore, Ocuserts offer the benefit of minimising the risk of systemic side effects. Since the drug is released directly into the eye and its exposure to the systemic circulation is limited, the potential for systemic adverse effects is reduced. This localised drug delivery approach helps to maximise the therapeutic effect within the eye while minimising systemic exposure. By providing extended drug release and controlled drug concentrations in the eye, Ocuserts offer a promising approach for ocular drug delivery. They allow for better management of ocular conditions by maintaining therapeutic drug levels for a longer duration and reducing the frequency of administration. Ongoing research and development in this field aim to further optimise the design and performance of Ocuserts to enhance their effectiveness and applicability in various ocular therapies.[3]

Ocular inserts are primarily classified into the following three kinds:

1. Ocular implants that are insoluble
2. Dissolvable eye implants
3. Bio erodible eye implants

### Insoluble Ophthalmic Implants

The insoluble inserts have been divided into three groups: hydrophilic contact lenses, osmotic systems, and diffusion systems.

In the first and second grades, it is in contact with a reservoir that dispenses medication to the rate controller's interior surface. The reservoir contains a liquid, thick, colloid, semisolid, hard matrix, or a drug carrier that is dispersed or dissolved therein in a homogenous or heterogeneous manner. Transporters may be made of materials that are organic, inorganic, synthetic, naturally occurring, hydrophobic, or hydrophilic.[4]

Contact lenses are included in the third class. The fundamental drawback of these devices is that they are insoluble, necessitating removal after usage.

### Diffusion Inserts

Due to the semi-permeable or microporous membranes that surround the central reservoir of the diffusion systems, the drug diffuses through it at a carefully calibrated rate. By creating enough internal pressure to force the medication out of the reservoir, the lachrymal fluid in such a system permeates the membrane to regulate the release of the drug. The rate at which medications are given is controlled

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through controllable diffusion through the membrane.[5]

## Osmotic Inserts

Osmotic inserts come in two main categories; the first category has a central area that is surrounded by a peripheral. A single reservoir or two separate compartments could make up the first central component. The first kind entails spreading a medication with or without the inclusion of an extra osmotic solution over a polymeric matrix to create discrete, minuscule drug deposits on the polymer.

In the case of ocular inserts with osmotic drug delivery mechanisms, the drug reservoir and osmotic solute reservoir are separated into distinct compartments. The osmotic inserts employ a semi-permeable membrane as the covering film, which is made of an insoluble polymer. This membrane allows for the diffusion of tear fluid into the peripheral deposits of the insert, leading to moistening and subsequent disintegration.

As the peripheral deposits dissolve, they generate hydrostatic pressure, which causes the polymeric matrix of the insert to swell. This swelling effect leads to the release of the drug from the matrix. The characteristic osmotic component of these inserts results in a zero-order drug release profile, meaning that the release rate remains constant over time.

The use of an osmotic solute reservoir and the controlled swelling of the polymer matrix allow for precise control of drug release. By modulating the osmotic pressure and the characteristics of the semi-permeable membrane, the release rate of the drug can be tailored to achieve the desired therapeutic effect.

The osmotic ocular inserts offer several advantages. They provide controlled and sustained drug release, ensuring a consistent drug concentration in the eye over an extended period. This allows for reduced dosing frequency and improved patient compliance. The zero-order release profile eliminates the need for frequent dosage adjustments, providing a more predictable and stable drug release pattern.

Overall, ocular inserts with osmotic drug delivery mechanisms provide an effective means of achieving prolonged drug release and maintaining therapeutic drug levels in the eye. Their design and functionality contribute to improved treatment outcomes and patient comfort in ophthalmic therapy.[6]

## Osmotic Insert Components

Osmotic substances are compounds that can create an osmotic pressure gradient when dissolved in a solution, which can be utilised in various pharmaceutical applications, including ocular dosage forms.

Ethylene-vinyl esters copolymers, polyethene, cross-linked polyvinylpyrrolidone (PVP), and plasticised polyvinyl chloride (PVC) are examples of water-permeable materials.

Cellulose acetate derivatives, Ethyl Vinyl Acetate (EVA), and Polyesters of Acrylic and Meth acrylic Acids (Eudragit) are examples of semi-permeable membranes.

Here are the examples you provided categorised by their chemical nature:

- Inorganic Osmotic Substances: e.g., magnesium sulphate, sodium chloride, potassium phosphate dibasic, sodium carbonate and sodium sulphate
- Organic Osmotic Substances: e.g., tartaric acid, magnesium succinate, and calcium lactate
- Carbohydrate Osmotic Substances: e.g., sorbitol, mannitol, glucose, and sucrose

These substances can be used in different ocular dosage forms such as eye drops, ointments, or ocular inserts to achieve desired osmotic effects. They can help regulate the osmolarity of the formulation, control drug release, enhance absorption, or provide a suitable environment for ocular tissues.

It's important to note that the selection of osmotic substances in ocular formulations should consider factors such as compatibility with other formulation components, desired osmotic effect, safety for ocular administration, and stability of the final product.

## Soft Contact Lenses

Soft contact lenses are three-dimensional networks or matrices that may hold onto water, aqueous solutions, or solid substances. They are made of covalently cross-linked hydrophilic or hydrophobic polymers. While a hydrophilic contact lens will absorb a drug solution, other non-soluble ophthalmic systems will be able to administer the medication more precisely. The drug release from such a device often starts quite quickly and then gradually slows down dramatically over time. A hydrophobic component or homogeneous medication incorporation during manufacturing can both reduce the release rate. Certainly, contact lenses have a bright future as ophthalmic drug delivery systems.[7]

## Soluble Ophthalmic Inserts

The soluble ophthalmic inserts represent one of the oldest classes of ocular inserts, offering the advantage of complete solubility without the need for removal after application. This minimises interventions to the simple act of insertion. These inserts can be classified based on the type of polymers used, either natural or synthetic/ semi-synthetic.

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**Based on Natural Polymers**

Some soluble ophthalmic inserts are composed of natural polymers, with collagen being one example. Collagen-based inserts have been used for various ocular applications due to collagen's biocompatibility, biodegradability, and similarity to ocular tissues. These inserts can release therapeutic drugs over a specific period as they dissolve in tears.

**Based on Synthetic or Semi-Synthetic Polymers**

Soluble ophthalmic inserts can also be formulated using synthetic or semi-synthetic polymers. These polymers provide flexibility in terms of design and drug release characteristics. Examples of synthetic polymers commonly used in ocular inserts include polyvinyl alcohol (PVA), polyethene glycol (PEG), and polylactic acid (PLA). These inserts can be tailored to control drug release rates based on the specific needs of the drug and the therapeutic application.

To load therapeutic drugs into soluble ophthalmic inserts, a common approach is to soak the insert in a drug-containing solution, followed by drying and rehydration before application.

## Factors Affecting Drug Loading

Several factors can affect the drug loading efficiency and release profile:

**Concentration of Drug Solution:** The concentration of the drug solution used for soaking the insert can influence the amount of drug loaded. Higher concentrations may result in increased drug loading, but there may be limitations based on the solubility of the drug in the chosen solution.

**Amount of Binding Agent:** The choice and amount of binding agent used in the insert formulation can affect drug loading. Binding agents help in retaining the drug within the insert structure and can impact the overall drug-loading capacity.

**Length of Soaking:** The duration of the soaking process can impact drug loading. Longer soaking times may allow for better drug penetration and incorporation into the insert matrix.

**Amount of Drug Loaded:** The quantity of drug incorporated into the insert can influence the overall drug release characteristics. The amount of drug loaded should be optimised to achieve the desired therapeutic effect without compromising safety or causing adverse effects.

It is important to consider the physicochemical properties of the drug, compatibility with the chosen polymers, and the desired release profile when formulating soluble ophthalmic inserts. Formulation optimisation and careful consideration of these factors can help ensure effective drug delivery and therapeutic outcomes.

The synthetic/ semi-synthetic polymer-containing soluble ophthalmic inserts have the added benefit of having a generally straightforward design.

- On successfully marketed products for ophthalmic use
- Easily processed using standard techniques including compression, injection moulding, or slow-evaporating extrusion

The medication is released from such a system by tearing through the insert, which causes the drug to diffuse out and form a gel layer around the insert's core. This external gelation causes the drug to diffuse out even more but is still controlled by diffusion. The following expression is obtained by deriving the release rate, J, from Fick's law.

$$J = -D\frac{d\Phi}{dx}$$

Where J: Diffusion flux; D: Diffusivity; dΦ: change in the concentration of the particle dx: change in the position is the membrane's surface; and dΦ/dx: concentration gradient of the particle.

The device's release rate remains constant while every requirement on the right side of the equation is met. One of the additional factors affecting the release of the medication from these Ocuserts is as follows:

- Inclusion diffusion
- The matrix swells
- The medication and the polymers dissolve
- The polymeric chain is relaxed

The soluble insert made of cellulose derivatives can be sterilised with gamma radiation without affecting the cellulose components. The release rate can be decreased by using a matrix polymer commonly used for enteric coatings or by including enough of a hydrophobic polymer, which, when added in the right proportion, can lessen the drug release while maintaining the solubility of the insert.

## Synthetic Polymer-Containing Soluble Inserts' Parts

**Synthetic Soluble Polymers**

- Derivatives of cellulose, including two types of cellulose exist: hydroxypropyl and hydroxyethyl cellulose.
- Ethylene vinyl acetate and polyvinyl alcohol copolymer are used by divers.
- Additives
- Propylene glycol, glycerin, and polyethene glycol make up the plasticizer.
- Hydroxypropyl methylcellulose and cellulose acetate phthalate are enteric-coated polymers. Agent for

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complexing. e.g., PVP.

- Polyacrylic acids are bioadhesives.[8]

## Biodegradable Ophthalmic Inserts

The components of the biodegradable inserts consist of a homogeneous drug dispersion, whether or not the drug is present, inside of a hydrophobic covering that is mostly impervious to the drug. 'Biodegradable' polymers were used in their construction. Orthoesters and orthocarbonates are two biodegradable polymers that are useful for ophthalmic use. The medication is released from the body when a device makes contact with tear fluid because it diverts the matrix for a moment.[9]

Indeed, the development and utilisation of solid ophthalmic devices have gained significance due to various factors. The introduction of new polymers has allowed for the design of novel ophthalmic inserts with improved drug-delivery properties. These polymers can provide a controlled release and enhanced stability of the incorporated drugs.

Furthermore, the emergence of new drugs with short biological half-lives or systemic side effects has necessitated the development of alternative delivery systems that can maintain effective drug concentrations in the eye over a prolonged duration. Solid ophthalmic devices, such as ocular inserts, offer a promising solution by providing sustained drug release and prolonged residence time in the eye.

By using solid ophthalmic devices, the efficacy of ophthalmic treatments can be enhanced. These devices allow for the maintenance of therapeutic drug levels in the eye, reducing the need for frequent administration and optimising treatment outcomes. The controlled release provided by solid devices ensures a consistent and prolonged drug concentration, leading to improved therapeutic effects.

The use of solid ophthalmic devices also offers advantages in terms of patient convenience and compliance. By reducing the frequency of dosing, these devices can simplify treatment regimens and enhance patient adherence to the prescribed therapy.

Overall, the increased utilisation of solid ophthalmic devices is driven by the need for improved drug delivery systems that can overcome the limitations of conventional liquid formulations. These devices provide extended drug release, enhanced drug stability, and increased patient convenience, contributing to the advancement of ophthalmic treatments.

## Advantages of Ocular Drug Delivery System

- The merits of the ocular drug delivery system are as follows:[10]
- Fewer doses are administered, leading to higher patient compliance.
- Extended contact, which boosts bioavailability.
- Systemic side effects can be reduced, which will lessen the negative effects.
- Accurate dosing: Unlike eye drops, which the patient may administer wrongly and which may lose some of their efficacy after delivery, each insert may be produced to contain a particular amount that is retained at the administration site.
- The possibility of using non-corneal (conjunctival sclera) pathways to reach internal ocular structures.
- Forbidding the use of preservatives to lower the likelihood of allergic responses.
- The ability to use various cutting-edge chemical and technological methods.

**Table 1.Past Work Done on Ocular Dosage Form by Quality by Design (QbD)**

| Drug | Dosage Form | Design | Independent Variables | Dependent Variables |
|---|---|---|---|---|
| Ciprofloxacin[11] | 3D-printed ocular inserts | Full factorial design (FFD) | Hydroxypropyl methylcellulose polymer (HPMC) ($X_1$) | In vitro release (DR) ($Y_1$), antibacterial activity (ABA) ($Y_2$), Transcorneal permeation (TP) in ex-vivo ($Y_3$), and stability of insert ($Y_4$) |
| Bromfenac[12] | Cubosomes | $2^3$ FFD | Glyceryl monoolein ($X_1$), poloxamer 407 ($X_2$), and polyvinyl alcohol (PVA) ($X_3$) | Entrapment efficiency (EE) ($Y_1$), zeta potential (ZP) ($Y_2$), particle size (PS) ($Y_3$), polydispersity index (PDI) ($Y_4$) |
| Brimonidine tartarate[13] | Gel | $3^2$ FFD | Tween 80 ($X_1$) and pluronic F68 ($X_2$) | PS ($Y_1$), ZP ($Y_2$) and EE ($Y_3$) |

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|---|---|---|---|---|
| Travoprost (prostaglandin analog)[14] | Gel | $3^2$ FFD | Sodium deoxycholate ($X_1$), lecithin ($X_2$) and cholesterol ($X_3$) | Permeation enhancer (PE) ($Y_1$), (EE) ($Y_2$), vesicle size (VS) ($Y_3$), PDI ($Y_4$) |
| Moxifloxacin HCl[15] | Ocular inserts | $2^3$ CCD | Eudragit FS-100 (FS) ($X_1$) and propylene glycol (PG) ($X_2$) | Drug release (DR) at 2h ($Y_1$), DR at 6 h ($Y_2$) |
| Quinuclidine[16] | Nan materials | $3^2$ FFD | Soybean oil ($X_1$), % glycerol ($X_2$) and the amplitude of sonication ($X_3$) | PS ($Y_1$), (PDI) ($Y_2$) and ZP ($Y_3$) |
| Methazolamide[17] | Gel | $2^3$ FFD | Oil type ($X_1$) oil/ total lipid % ($X_2$) and Span 80 ($X_3$) | EE ($Y_1$), PS ($Y_2$), PDI ($Y_3$), and ZP ($Y_4$) |
| Fenticonazole nitrate[18] | Ocular insert | $3^2$ FFD | Terpenes type ($X_1$) and terpenes amount ($X_2$) | (EE) ($Y_1$), (PS) ($Y_2$) and (PDI) ($Y_3$) |
| Fluorescein sodium[19] | Microneedles | CCD | Gantrez S-97 ($X_1$) and hyaluronic acid (HA) ($X_2$) | Mechanical strength (MS) at 20 N($Y_1$), drug permeation (DP) in 24 hours ($Y_2$) |
| Voriconazole[20] | Ocular mucoadhesive cubosomes | CCD | Monoolein ($X_1$) and pluronic F-127($X_2$) | PS ($Y_1$), ZP ($Y_2$), drug content (DC) ($Y_3$), EE ($Y_4$) and DC ($Y_5$) |
| Nepafenac[21] | Ocular insert | $3^2$ FFD | Soluplus VR ($X_1$) and the plasticizer, and PEG-400 ($X_2$) | DR in 4 h ($Y_1$) and tensile strength (TS) ($Y_2$) |
| Natamycin[22] | Eye-drops | $2^3$ FFD | Precirol ATO 5 ($X_1$), Span80 ($X_2$), and castor oil ($X_3$) | (PS) ($Y_1$), PDI ($Y_2$), $EE_{min}$ ($Y_3$), $EE_{max}$ ($Y_4$) |
| Sulfoxyamine[23] | Ocular inserts | $3^2$ FFD | (PVA) ($X_1$) and Chitosan (C) ($X_2$) | Moisture absorption (MA) ($Y_1$) and MS ($Y_2$) |
| Acyclovir[24] | Gel | $2^3$ FFD | Soya-lecithin (SL) ($X_1$) and Chitosan ($X_2$) | PS ($Y_1$), DR ($Y_2$), EE ($Y_3$) |
| Chloramphenicol[25] | Gel | $3^2$ FD | Poloxamer 407 ($X_1$) and (HPMC) ($X_2$) | Gelling capacity (GC) ($Y_1$), pH ($Y_2$) and viscosity ($Y_3$) |
| Besifloxacin HCl[26] | Liposomal gel | $3^2$ FFD | SL ($X_1$) and cholesterol ($X_2$) | Drug loading ($Y_1$), (PS) ($Y_2$), and encapsulation effectiveness (EE) ($Y_3$) |

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|---|---|---|---|---|
| Timolol maleate[27] | Polymeric nanoparticles | $2^3$ CCD | Flax seed gum (FX) ($X_1$) and chitosan ($X_2$) | PS ($Y_1$) and EE ($Y_2$) |
| Natamycin[28] | Gel | $2^3$ FD | Boric acid ($X_1$), Carbopol 940 ($X_2$), and Guar gum ($X_3$) | GC ($Y_1$), Gel depot collapse time ($Y_2$), viscosity ($Y_3$), Firmness ($Y_4$), and MS ($Y_5$) |
| Dorzolamide HCl[29] | Ocular drug insert | $3^2$ FFD | Poloxamer 407 ($X_1$) and PG ($X_2$) | DR ($Y_1$) and TP ($Y_2$) |
| Dorzolamide-HCl[30] | Proniosomal gel | $5^2$ FFD | Cholesterol ($X_1$) and surfactant (Span 40) ($X_2$) | EE ($Y_1$), PS ($Y_2$), and DR at 8h ($Y_3$) |
| Dexamethasone sodium phosphate and chloramphenicol[31] | Gel | $3^2$ FFD | Carbopol 940 ($X_1$), gum of gellan ($X_2$) | DR ($Y_1$), DR at $t_{90\%}$ t ($Y_2$), PR ($Y_3$), mucoadhesive strength (MS) ($Y_4$), viscosity ($Y_5$), and viscosity ($Y_6$) |
| Lomefloxacin HCl[32] | Noisomal encapsulation | $3^2$ FFD | Surfactant ($X_1$) and cholesterol ($X_2$) | EE ($Y_1$), PS ($Y_2$) and ZP ($Y_3$) |
| Propranolol HCl[33] | Nanostructure lipid carrier | $2^3$ FFD | Surfactant/ lipid ($X_1$), liquid/ lipid ($X_2$) and transcutol ($X_3$) | DR ($Y_1$), and EE ($Y_2$) |
| Prednisolone[34] | Nanoparticles-laden contact lens | Statistical experimental design | Poly DL-lactic co-glycolic acid (PLGA) ($X_1$), and PVA ($X_2$) | DR ($Y_1$) and homogenisation time ($Y_2$) |
| Loteprednol etabonate[35] | Ophthalmic gel | $3^2$ FD | Capryol 90 ($X_1$), Tween 80 ($X_2$) and transistor P (co-surfactant) ($X_3$) | EE ($Y_1$) and DR ($Y_2$) |
| Cyclosporine-A[36] | Inserts | $2^3$ FFD | HPMC ($X_1$) and xanthan gum ($X_2$) | Drug content($Y_1$), MA and loss ($Y_2$), and surface pH($Y_3$) |
| Dorzolamide HCl[37] | Gel | $3^2$ FFD | HPMC K15 M ($X_1$) and Poloxamer 407 ($X_2$) | Gelation temperature (GT) ($X_1$), viscosity ($X_2$) and DR ($X_3$) |
| Levofloxacin hemihydrates[38] | Ocular semi-sponges | $3^2$ FFD | Gel rite ($X_1$), Chitosan ($X_2$), and sodium carboxymethylcellulose ($X_3$) | DR ($Y_1$), and $t_{50}$ ($Y_2$) |
| Clonidine HCl[39] | Gel | $2^2$ FFD | Poloxamer 407 ($X_1$), and HPMC K15M ($X_2$) | GT ($X_1$), DC ($X_2$), MS ($X_3$), viscosity ($X_4$) and DR ($X_5$) |
| Moxifloxacin HCl[40] | Gel | $3^2$ FFD | Carbopol ($X_1$) and HPMC ($X_2$) | $t_{50\%}$($Y_1$) and DR ($Y_2$), DC ($Y_3$), viscosity ($Y_4$), and gel strength ($Y_5$) |

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| | | | | |
|---|---|---|---|---|
| Cyclosporine A[41] | Films | $2^4$ FFD | Chitosan ($X_1$) | Thickness ($Y_1$), swelling index ($Y_2$) and mechanical properties ($Y_3$) |
| Acyclovir[42] | Nanoparticles | $3^2$ FFD | Drug to polymer ratio ($X_1$) and the amount of electrolyte ($X_2$) | PS ($Y_1$) and EE ($Y_2$) |
| Clotrimazole[43] | Nanovesicles | $3^2$ FFD | Tween 80 ($X_1$), and sodium cholate ($X_2$) | PS ($Y_1$), EE ($Y_2$) and ZP ($Y_3$) |
| Cetyl trimethylammonium bromide[44] | Lipid nanoparticles | $3^3$ FFD | Lecithin (Lipoid S75) ($X_1$) and hydrophilic surfactant P188 ($X_2$) | PS ($Y_1$), PDI ($Y_2$) and ZP ($Y_3$) |
| Nebivolol HCl[45] | Dissolving films | Simplex lattice design | HPMC ($X_1$), pullulan ($X_2$) and polyvinyl pyrrolidone (PVP) ($X_3$) | DR ($Y_1$), TS ($Y_2$), elastic modulus ($Y_3$), and % elongation ($Y_4$) |
| Cyclosporine[46] | Nanoparticles | $2^3$ FFD | Chitosan ($X_1$) | DR ($Y_4$), ZP ($Y_3$), PDI ($Y_2$), and PS ($Y_1$) |
| Acyclovir[47] | Ocular insert | $3^3$ FFD | Methylcellulose ($X_1$), PVP ($X_2$) and PVA ($X_3$) | %CDR ($Y_1$), Folding Endurance ($Y_2$) and thickness ($Y_3$) |
| Timolol maleate[48] | Ocular insert | $3^2$ FFD | Eudragit ($X_1$), (HPMC) ($X_2$) | DR at 12h ($Y_1$), DR at 18h ($Y_2$), and $t_{50\%}$ ($Y_3$) |
| Tropic amide[49] | Nanoparticles | $3^2$ CCD | Carboxymethyl tamarind kernel polysaccharide ($X_1$) and calcium chloride ($X_2$) | PS ($Y_1$) and % EE($Y_2$) |
| Gatifloxacin[50] | Ophthalmic gels | $3^2$ FD | Carbopol 974P ($X_1$) and oloxamer 407 ($X_2$) | GT ($Y_1$), gel strength ($Y_2$), bio adhesion ($Y_3$), viscosity ($Y_4$), DP ($Y_5$) and ABA ($Y_6$) |
| Fluconazole[51] | Nanoparticles | $2^3$ FFD | Poloxamer P407 ($X_1$), and sonication time ($X_2$) | EE ($Y_1$), PS ($Y_2$), and ZP ($Y_3$) |
| Brimonidine tartrate[52] | Ocular inserts | $3^2$ FD | Cellulose acetate butyrate ($X_1$), PEG-600 ($X_2$) | DR at 24 h ($Y_1$), first-order rate constant ($Y_2$), and $t_{50\%}$ ($Y_3$) |
| Norfloxacin[53] | Gel | $3^2$ FFD | HPMC K-100-M ($X_1$) and pluronic-F-127 ($X_2$) | DR ($Y_1$) and viscosity ($Y_2$) |

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- The past successful attempts on ocular dosage form by Quality by Design (QbD) were as per Table 1.

## Conclusion

Ocular inserts are useful because they reduce the risks associated with pulsed dosing of conventional dosage forms, decrease drug loss, and increase patient compliance. Additionally, they provide medications in a regulated and maintained manner while enhancing bioavailability and corneal contact duration.

The achievement of an efficient medication concentration at the anticipated location of action for the specified amount of moment is the aim of pharmacotherapy. In order to reduce the danger of eye injury from high blood medication concentrations, local therapy rather than systemic therapy is typically chosen as a portal for drug administration.

Major drawbacks of the traditional ocular dose forms, such as eye drops and ointments, include:

- Poor bioavailability because of quick precorneal elimination, typical tear turnover, and conjunctival absorption
- Repeated administration of potent drugs
- Unfavourable side effects of drug systemic absorption
- Vision blurring due to viscous cars.

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