New Advances in ocular inserts: A nod to nanotechnology

Sura Zuhair Mahmood*, Athmar Dhahir Habeeb Al-Shohani*
Department of Pharmaceutics, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.

Article Info:

Received 10 May2024
Revised 10 Aug 2024
Accepted 29 Aug 2024
Published 31 Aug2025
Corresponding Author email:
Athmar1978@uomustansiriyah.edu.iq
Orcid: https://orcid.org/0000-0002-4690-5660

DOI: https://doi.org/10.32947/ajps.v25i3.1190

Abstract:

Ocular drug delivery is an interesting and unique field for formulation scientists because of the many physiological and anatomical barriers of the eye. Although the eye is easily available for topical application only low amount of the administered dose reach the ocular tissues. Most of the applied medication, in particular eye drops which comprise 90% of all ocular medications, easily removed by blinking, excessive tearing, nasolacrymal drainage and corneal barriers.

Enhance pre-corneal residence time in ocular tissues is required to enhance bioavailability and reduce instillation time. Among the strategies used to enhance pre-corneal residence time is using ocular inserts. They are sterile solid or semisolid preparations that usually placed in cul-de-sac of the conjunctiva to increase pre-corneal residence time of the loaded drug. They must be formulated at specific thickness, shape and size to avoid eye irritation once applied. They can also be used for sustained drug delivery to the eye and the possibility of application of more than one drug at the same time. In this review we will look into the types of inserts, mechanism of drug release from the inserts and their advantages and disadvantages. In addition, we will have a deep look into how nanotechnology improved ocular inserts and the new advances in this field.

Key words: ocular inserts, nanotechnology, ocusert, bioadhesion

التطورات الجديدة في الإدخالات العينية: إضافة إلى تكنولوجيا النانو لهذا المجال

أثمار ظاهر حبيب* سرى زهير محمود*
**** فرع الصيدلانيات، كلية الصيدلة، الجامعة المستنصرية، بغداد، العراق.***

خلاصة

يعد توصيل الأدوية عن طريق العين مجالًا مثيرًا للاهتمام وفريدًا من نوعه لعلماء تحضير التراكيب بسبب وجود العديد من الحواجز الفسيولوجية والتشريحية للعين. على الرغم من أن العين متاحة بسهولة للاستخدام الموضعي، إلا أن كمية قليلة من الجرعة المعطاة تصل إلى أنسجة العين. معظم الأدوية المستخدمة، وخاصة قطرات العين التي تشكل 90٪ من جميع الأدوية المستخدمة للعين، يمكن إزالتها بسهولة عن طريق الرمش، وافرازالدمع المفرط، والتصريف الأنفي الدمعي، وحواجز القرنية. يعد تعزيز وقت الإقامة قبل القرنية في أنسجة العين أمرًا ضروريًا لتعزيز التوافر البيولوجي وتقليل وقت التقطير. من بين الاستراتيجيات المستخدمة لتعزيز وقت الإقامة قبل القرنية باستخدام الاقراص الصلبة العينية. وهي عبارة عن مستحضرات صلبة أو شبه صلبة معقمة يتم وضعها عادةً في طريق الجفن الداخلي لزيادة وقت بقاء الدواء المحمل قبل القرنية. ويجب صياغتها بسماكة وشكل وحجم محددين لتجنب تهيج العين بمجرد تطبيقها. كما يمكن استخدامها لإيصال الدواء بشكل مستدام إلى العين وإمكانية ايصال أكثر من دواء في نفس الوقت. في هذه المراجعة سننظر في أنواع الاقراص الصلبة وآلية إطلاق الدواء منها

ومزاياها وعيوبها. بالإضافة إلى ذلك، سنلقي نظرة عميقة على كيفية تحسين تقنية النانو للأقراص الصلبة العينية والتطورات الجديدة في هذا المجال.

الكلمات المفتاحية: المدخلات العينية، تقنية النانو، الأوكوسرت، الالتصاق الحيوي

Introduction

The field of ocular drug delivery is unique and one of the most interesting and challenging fields in the area of localized drug delivery. The eye is an open organ that is easily accessible and convenient to be used by the patients without external help. Due to the open nature of the eye, it is impervious to foreign bodies through different defense mechanisms, which are considered as barriers for a successful ocular delivery. For a formulation scientists, the challenge is to overcome the many anatomical and physiological barriers of the eye to deliver an effective treatment (1–3).

The main barrier is the cornea due to its lipophilic nature and complex structure. It is a transparent layer that covers the front of the eye and consist of three main layers, epithelium, endothelium and stroma, separated by two membranes. Each layer has a different structure, physiological properties and lipophilicity which hinder the transport of the drug through the cornea. The lipophilic nature of the epithelium along with the tight junctions between the cells represent a barrier for paracellular and transcellular transport of hydrophilic drugs. On the other hand, the hydrophilic nature of the stroma also hinders the permeation of topically administered hydrophobic drugs(4–7).

Followed instillation of an eye drop reflex blinking, excessive tear production and nasolacrimal drainage play a role in reducing efficiency of treatment. They tend to dilute and wash any foreign materials on the topical surface within minutes thus reduce the pre-corneal residence time. That is why only 5% of an instilled eye drop penetrate to the ocular tissues and the rest is eliminated through nasolacrimal drainage and the conjunctival blood circulation. Frequent daily administration is required with eye drops to maintain the therapeutic level of the applied medication at the site of action. Frequent administration is one of the reasons for low adherence to treatment when treating ocular diseases especially when treating chronic conditions such as glaucoma. Another concern is the continuous exposure of the ocular tissues to preservatives which will increase sensitivity of ocular tissues with continues exposure (8–10).

Increasing pre-corneal residence time (PCRT) is a key factor that will allow the drug to remain in contact with ocular surfaces for extended period, thus improving efficacy and bioavailability of the applied medication and reducing instillation times. Increasing PCRT through different strategies was investigated and many approaches were evaluated such as enhancing viscosity, use of mucoadhesive formulations, collagen shields, *in-situ* formulations, nanoformulations, vesicular systems, mini tablets, therapeutic contact lenses and ocular inserts (11–19) .

Ocular inserts are sterile solid or semisolid preparations that are used for the delivery of drugs to ocular tissues. They are usually placed in cul-de-sac of the conjunctiva to increase PCRT of the loaded drug. They must be formulated at specific thickness, shape and size to avoid eye irritation once applied. Some of their advantages, in addition to increase PCRT, includes the elimination of the need to use preservatives, accurate dosing, minimize dosing intervals, improved

patient adherence to treatment, better control of drug release and the possibility of application of more than one drug at the same time (20–23).

Historical background

The use of inserts is dated back to the 1800s when drug impregnated filter paper was cut and placed in the conjunctiva. However, inserts in its modern form was first introduced in the seventies(24,25). In 1975 pilocarpine ocusert was introduced as a controlled release dosage form. They were placed in the conjunctival sac and formulated to deliver pilocarpine for one week for the treatment of glaucoma. When compared to eye drops, ocular residence time and efficacy were good. But there was a problem of sudden leakage of pilocarpine encountered in some patients involved in the study (26,27). Another example of research conducted at that period is an artificial tear insert formulated for the treatment of dry eye. A soluble succinylated collagen insert was placed in the cul-de-sac to slowly release the polymer instead of frequent instillation of artificial eye drops. When evaluated in patients no report of blurred vision or discomfort was recorded (28).

Some researchers use Four different mucoadhesive polymeric film formulations containing ERY-loaded EUD/PVA nanoparticles were designed and developed as ocular inserts to overcome the trials related to the administration of conventional eye formulations including limited bioavailability, short residence time, and the necessity of frequent administration. The researchers supposed that these formulations have the potential to be more developed and evaluated for delivery of various topical ocular agents such as antibiotics, antifungals, ocular hypotensive, steroids and nonsteroidal anti-inflammatory, antihistamines, decongestants etc.(29),

Research continued over the next two decades and several published research articles reported successful attempts in formulating ocular inserts(30–32). An example of the research conducted at that period is the fabrication of hydroxypropyl cellulose insert. The insert, measuring approximately 3x 1 mm, was placed in patient fornix for the treatment of dry eyes. Patients involved in the study reported good tolerance with only few experiencing problems (33). From that period onward the research on ocular inserts gain momentum and development were made regarding the formulation techniques and polymers used(34–37).

Requirements of a typical ocular inserts (38)

1- Must be biocompatible to ocular surfaces.
2- Must be stable, nontoxic, non-immunogenic and non-carcinogenic.
3- Release of the drug in a controlled manner and for extended period is favorable.
4- For non-biodegradable must be easy to retrieve if problems detected or after use.
5- Do not cause discomfort or blurred vision upon use.
6- Should have good mechanical strength and durability.
7- Easy to manufacture and sterilize to minimize cost.
8-

General problems encountered with ocular inserts

There are general problems associated with ocular inserts which includes (38):

1. Discomfort during application and use especially in oversensitive patients.
2. If not mucoadhesive they tend to move around the eye with possibility

of loss during sleep or rubbing the eye.
3. May cause blurred vision.
4. Difficulty in removal for insoluble inserts and difficulty in controlling the release of incorporated drugs for soluble inserts.

Mechanisms of drug release from inserts

Drug incorporated into the insert will be release by three main mechanisms; diffusion, bioerosion and osmosis.

1- Diffusion

It is the process of transfer of drug molecule from one part to the other depending on the concentration gradient. In the case of ocular inserts the drug will diffuse from the insert into the surrounding lachrymal fluid from either soluble or insoluble insert. In the matrix form of insoluble inserts, the drug is dispersed in the non-biodegradable polymer matrix and the surface of the matrix is usually surrounded by a porous membrane. Once placed in the eye, the water from the tear film will enter the matrix and dissolve the drug which will diffuse through the pores in a controlled manner(40–42).

For soluble inserts the swelling of the polymer is the key factor for dissolution and controlled the diffusion of the drug. The drug is homogenously dispersed in a polymer matrix and once placed in the eye they start to swell followed by diffusion of the drug(42). The swelling of the polymer depends on the physicochemical properties of the polymer used. When hydroxypropyl methylcellulose or polyvinyl alcohol were used for the preparation of cetirizine hydrochloride insert the matrix the type of the polymer had an effect on mechanism of drug released. Since both are hydrophilic polymers with tendency to swell the release of the drug was through diffusion from the swelling matrix(43).

2- Bioerosion

When an insert formulated with biodegradable polymers the release of the incorporated drug will be through bioerosion mechanism. The drug is usually dispersed in a bioerodable matrix. Once placed in contact with tear film the inserts starts to erode and release the drug. The rate of drug release is controlled by the rate of erosion of the polymer which depends on the physicochemical properties of the polymer used. Chemical or enzymatic hydrolytic reaction is responsible for erosion. The advantages of bioerodible inserts is the ability to modulate their erosion patterns to control the release or improve physical properties of the insert (44,45).

3- Osmosis

Drug released through osmosis when incorporated into insoluble insert. It is usually formulated with two compartments separated by an impermeable elastic membrane. The first compartment, which contain an osmotic solute, is surrounded by semi-permeable membrane in addition to the impermeable elastic membrane. The solute must not pass through the semi-permeable membrane. The second compartment, which is considered as the reservoir for the drug, is surrounded by impermeable and elastic membrane. An aperture for the release of the drug is present in the impermeable membrane of the insert. The reservoir of the drug could be in liquid or gel form. Once in contact with tear film, water will diffuse to the first compartment and extends the elastic membrane to inflate the first compartment. Once inflated the first compartment will shrink the second compartment and forces the drug through the aperture (46).

Classification of ocular inserts

Ocular inserts can be classified according to their fate after application into soluble and insoluble inserts.

A) Soluble inserts

They are the oldest class of inserts that are designed to be dissolved completely during use to eliminate the need for removal after application. They are also known as degradable and biodegradable based on the type of polymer used. Depending on the drug release mechanism (diffusion or bioerosion) water soluble polymers or bioerodible polymers are used for their manufacture. Several polymers were utilized such as collagen, polyethylene oxide, cellulose derivatives, polyvinyl alcohol, polyester derivatives, polycaprolactone, poloxamers and soluplus (47–50).

Patil et al reported the preparation of dorzolamide hydrochloride soluble ocular insert using polyvinyl alcohol and poloxamer 407. The release of the drug was sustained for 6 h with complete solubility of the insert (51). Nepafenac ocular insert using soluplus as insert forming polymer was also prepared. The insert had a proper physical and chemical properties and had sustained the release for around 4 h (52).

As noticed with previous examples the main problem encountered with soluble inserts is their rapid solubilization by the lachrymal fluid and difficulty in controlling the release of the drug. Approaches such as incorporation of hydrophobic polymers and mucoadhesive polymers in the formulation were introduced to provide a more controlled environment for the release of the drug(47,53).

Freeze-dried solid inserts for the delivery of hLF 1-11 peptide was fabricated with mucoadhesive polymers hydroxypropyl methylcellulose and sodium hyaluronate. Only 40% of the drug was released within 4 hours and the remaining amount was sustained (54). Abdelkader et al reported the impact of mucoadhesion on curcumin release from an insert. The insert was formulated using a mucoadhesive polymers (carboxymethylcellulose, polyvinyl alcohol, hydroxypropyl methylcellulose) and thermoresponsive polymer pluronic F127. The *in vitro* release and trascorneal permeation were enhanced by 9 fold and 8.86-fold respectively when compared to a control curcumin suspension (55). Ofloxacin and dexamethasone were also formulated as matrix insert using bioadhesive hydroxy propyl methyl cellulose and biodegradable Eudragit at different concentrations and combinations. All formulas prepared sustained the release for 24 h and followed zero order kinetics (56).

Coating the insert with control releasing polymer was also investigated as a mean to control the release of incorporated drug from the prepared inserts (57). Pawar et al reported that when an insert of moxifloxacin formulated using sodium alginate and polyvinyl alcohol was coated with different grades of Eudragit, the release was modified. The uncoated insert sustain the release for 5 h compared to 9 h for the coated insert. In the *in vivo* study the permeation percent was 34.95% within 5 h without coating and significantly increased to 68.42% within 9 h after coating(58). Valarmathi et al reported the formulation of reservoir insert. A reservoir of hydroxyl propyl cellulose or polyvinyl alcohol and aciclovir was made by solvent casting method and coated with a rate controlling film of ethylcellulose or eduragit RL 100 at different concentrations. In the optimum formula only 10 % of the drug was released after 2 h and the release was sustained for 24 h with no irritation based on the animal study(59). Dawba also reported that coating a ciprofloxacin hydrochloride insert by release controlling membrane had

an impact on the release of the drug. The reservoir was formulated using pullulan or hydroxy propyl methyl cellulose and both were coated with hydroxy ethyl cellulose. Before coating 60% of the drug was released within 30 min and complete release achieved within 1 h. The coating of all formulations extended the release between 7 to 25 h based on the concentration of the coating used(60).
Two biodegradable ocular inserts are FDA approved; DEXTENZA® and LACRISERT®. Lacrisert is a biodegradable rode shape insert formulated using hydroxypropyl cellulose polymer which is used for the treatment of dry eye syndrome. The insert is 3.5 mm long with a 1.27 mm diameter and contain 5 mg of hydroxypropyl cellulose. It is preservative free and dissolves within 14-18 h after application in the inferior conjunctival cul-de-sac. It acts by stabilizing the precorneal tear film, lubricating the eye and prolonging the tear film breakup time(61,62).
Dextenza is a dexamethasone insert approved by FDA for the treatment of pain and inflammation after ophthalmic surgery. It is designed to be placed in the punctum of the eye to release dexamethasone for one month to ocular surfaces. The insert contains 0.4 mg dexamethasone and the release of the drug here depends mainly on the solubility of dexamethasone in the tear film(63).

B) Insoluble inserts

Insoluble inserts are solid or semi-solid preparations that consist of a drug reservoir squeeze in by rate-controlled polymers as part of a drug delivery system. In a container system, drugs that have been diffused or dissolved in a polymer matrix might be liquid, semi-solid, gel, or solid (29). As carriers, hydrophobic, hydrophilic, inorganic, organic, synthetic, natural, or other polymers can be employed
They are further divided into matrix and reservoir. The main problem associated with insoluble insert is the removal of the insert after use and the main advantage is better control of the release.

1- Reservoir system

In reservoir system the release is controlled by a rate controlling membrane and the drug is released either by diffusion or osmosis based on the method of fabrication. The drug in the reservoir could be either a liquid, gel, semisolid, colloid, solid matrix or drug carrier complex form (64,65). Ocusert is an example of diffusional insert that release a drug from a reservoir through microporous membrane at constant rate. As mentioned earlier, Ocusert pilo-20 and Ocusert pilo-40 were the first FDA approved ocusert for pilocarpine delivery for the treatment of glaucoma. They release the drug at a constant rate and provide near constant concentration of the drug in ocular tissues for 7 days. Lowering the side effect of the drug such as miosis and myopia was obtained. The reservoir is fabricated from alginic acid pilocarpine and surrounded by ethylenevinyl acetate rate controlling membrane and impregnated with titanium dioxide. The reservoir is surrounded by annular ring for visibility in insertion and removal of the insert(26,66).

2- Matrix system

It involves in incorporation of the drug into a crosslinked polymeric matrix fabricated using hydrophilic or hydrophobic polymers. The crosslinked matrix tend to swell to equilibrium and release the drug by diffusion. Contact lenses are considered as a type of insoluble matrix insert for ocular delivery in which the drug is incorporated into the lens and slowly release during the wearing of the lens. When first introduced contact lenses were used for vision correction and aesthetic use. However, over the years their use as drug

delivery system gained popularity because of their biocompatible nature to the eye (67–70). The duration of Moxifloxacin release from silicon contact lens was above the minimum inhibitory concentrations for 13 days (71). Maulvi et al reported the use of silicone contact lens for the delivery of gatifloxacin. The release of the drug was sustained for 48 h and further enhanced to 72 h when pluronic was used to enhance loading of the drug to the contact lens(72). Another research reported that travoprost release was sustained using contact lens. When the drug was loaded into the lens via soaking method from a solution the release was sustained for 36-48 h for the different formulations. And further improvement in release was observed when emulsion of the drug was used as soaking medium. The release was extended for 48-120 h (73).

New Advances in ocular inserts: the role of nanotechnology

Current research on ocular inserts is focusing on combining different approaches to overcome the problems associated with conventional formulations and further improve their properties. Several approaches were investigated over the years and some modifications can be seen in Table 1. However, the most widely investigated approach was the use of nanotechnology in ocular onserts.

Table 1: New advances in ocular insert formulations

Drug	Polymer used	modification	Improvement	Ref.
triamcinolone acetonide	Hydrophobic poly (1,4-butylene succinate) (PBS)	Plasma-assisted chemical surface functionalization of the PBS scaffolds made by electrospinning with biopolymers (inulin, α,β-poly(N-2-hydroxyethyl)-D,L-aspartamide, heparin)	improving surface hydrophilicity without modifying the bulk properties of the material and improving wettability, mucoadhesion and cyto- compatibility on human corneal epithelial cells	(74)
linezolid	Sodium alginate	Grafting the polymer Sodium alginate-grafted- poly (butyl methacrylate) and sodium alginate-grafted-poly (lauryl methacrylate) were synthesized.	Stronger adhesive force, slower release of the drug	(75)
pilocarpine nitrate	polyvinyl alcohol (PVA) as film-forming polymer blendedwith sodiumalginate, as bioadhesive polymer. The effect of addition ofeither carboxymethycellulose, carbopol, polyvinylpyrrolidone, or methylcellulose was investigated.	in situ film-forming liquids	convenient for patients	(76)

gatifloxacin	thiolated sodium alginate used for the preparation of mucoadhesive layer ol	Bilayered film in which one layer is mucoadhesive and the second layer is sustained release layer Eudragit RL 100 and Eudragit RS 100 in 75 : 25 proportion	The mucoadhesive film when used alone released 85% of the drug within 1 h however the bilayered film release 70% within 12 h	(77)

Nanotechnology is one of the technologies that found application in all aspects of life including medicine (78,79). It involves the manipulation of the structure of particles to nanoscale level (1-100 nm). In ocular delivery nanoformulations, such as nanoparticles, nanosuspensions, nanoemulsions and nanogels, helped to overcome ocular barriers by enhancing permeation through the cornea thus enhancing efficacy, minimize degradation of unstable drugs sustain the release of the loaded drug and increase ocular residence time through their ability to adhere to mucus tissues as a consequence of their small size (80–84). The formulation of the drug in nanoscale followed by incorporation into a solid matrix or formulate using advanced mechanisms such as electrospinning technique gained momentum in the past few years. The next paragraphs will discuss in details the benefit of combining nanotechnology and ocular inserts.

Electrospinning technique

It is a new and simple method for manufacturing of nanofibers with high productivity. It involves the transformation of a polymeric solution into a solid nanofiber by the use of high voltage electricity. Three main parts are involved in the process; power supply, spinneret (syringe) and a collector. A high voltage electricity is applied between the syringe and collector which are separated by an appropriate distance. When high voltage applied into the polymeric solution, charges accumulate at its surface and starts to repel each other to overcome the surface tension of the droplets and form a Tylor cone. From the tip of the cone a charged jet is ejected and moves to the collector which has an opposite charge. The jet then stretches in the electric field and the solvent evaporates and converts into a solid fiber. Nanofibers produced by this method have favorable properties such as flexibility, porous structure, enhanced mechanical strength and high surface area(85–87).

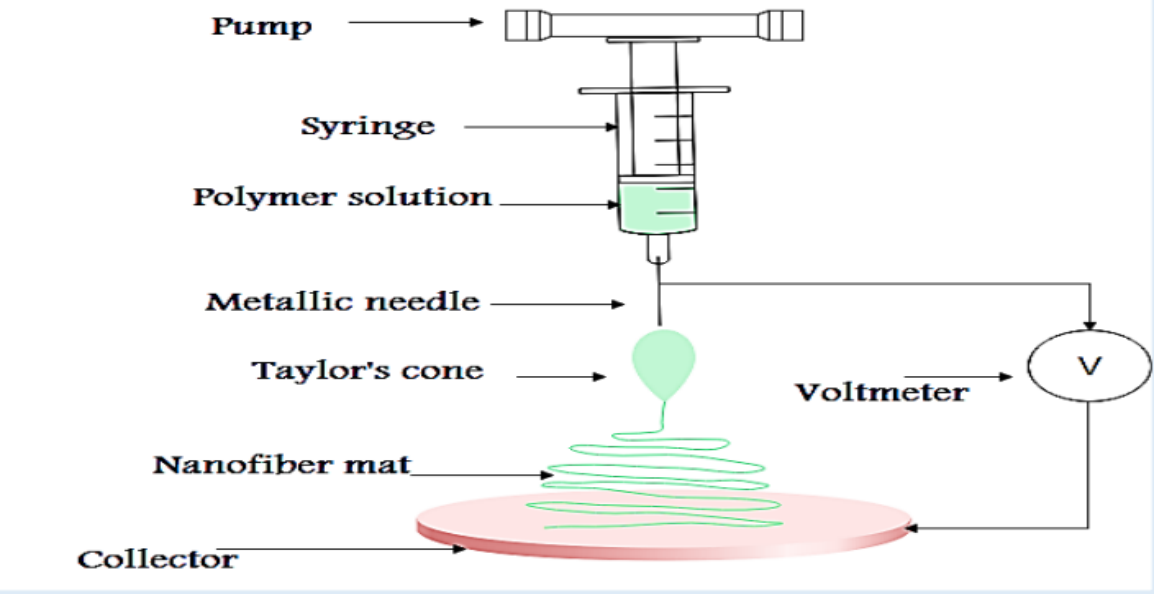

Figure 1. Diagram of electrospinning process (88)

Mirzaeei et.al reported the formulation of triamcinolone acetonide as nanofiber ocular insert. Chitosan formulations were compared to formulations fabricated using hydrophobic Eudragit S100 and Zein polymers. Burst release was not observed and the release continued for 4 days compared to free triamcinolone acetonide which released 70% within 8 h (89).

PEG and PCL were used for the formulation of electrospun nanofibers as ocular inserts for the delivery of besifloxacin HCl. Although the release was faster in the first two days it continued at fixed rate for 7 days until a 100% release was acheived (90).

Biodegradable polycaprolactone nanofibers loaded with fluocinolone acetonide were prepared as ocular insert using electrospinning technique. The insert demonstrated an extended release for up to 5 days which was reflected by the improvement in permeability and pharmacokinetics of the drug compared to drug suspension. As a result of improving residence time the half-life of the drug was 18.96 h for the insert compared to 4.6 h for the drug in suspension (91).

Insert loaded nanoparticles

Nanoparticles (NP) are particulate substances that have one or more dimentions that is less than 100 nm in diameter. When particles formulated in nanoscale their physical and chemical properties modified(92). They are broadly classifed into organic and inorganic NP based on the materials used for their synthesis Figure 1.

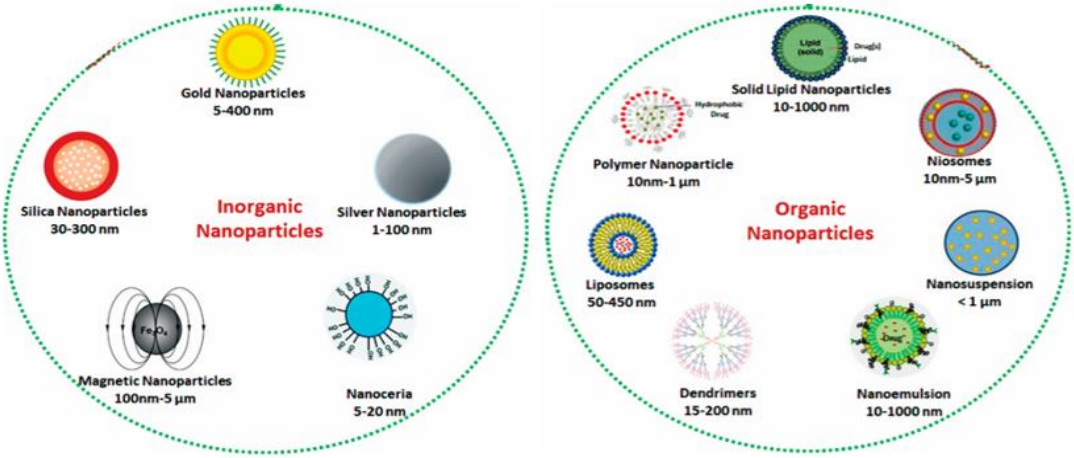

Figure 2 Classification of nanparticles (80).

The ocular inserts are used either as a platform for delivery of the NP or enhance the efficacy of NP through increasing PCRT. Mohammadi et al reported the preparation of Ketorolac tromethamine loaded eudragit nanoparticles for the treatment of ocular inflammation. The nanoparticles of the drug were prepared first then they were incorporated into polyvinyl alcohol and hydroxyethyl cellulose insert. The insert was prepared using different ratios of polyvinyl alcohol and hydroxyethyl cellulose. The optimum formula has a burst release of 18% within 4 h followed by extended release for up to 50 h and followed Higuchi model for release (93).

Another research on the release of Ketorolac tromethamine from nanodispersion loaded mucoadhesive ocular inserts was reported. Different grades of hydroxypropyl methylcellulose were compared as mucoadhesive polymer for the insert synthesis. The permeation of the drug was significantly higher compared to eye drops (94).

Azithromycin biodegradable mucoadhesive nanoparticles were formulated using poly (lactic-co-glycolic acid) copolymer/pluronic and later incorporated into a nanofiber insert. The insert was formulated using electrospun technique and polyvinylpyrrolidone as the main polymer. Azithromycin permeation was significantly enhanced and the release profile achieved for an azithromycin eye drop in 24 h was achieved for the insert in 10 days. The half-life was extended from 6.3 h to 93.5 h based on the pharmacokinetic studies(95).

Nanostructured lipid carrier approach was utilized for the formulation of ocular inserts. Nanostructured lipid carrier of ofloxacin was incorporated into a chitosan oligosaccharide lactate solid insert. The insert provided a sustained release for 24 h which render it suitable for one day application(96). Shukr reported that when voriconazole was prepared as niosomes and loaded into an ocular insert the release of the drug was sustaned for 8 h(97).

Another area of interest and was the focus of researchers for the past few years is loading NP into contact lens. The following table will shed light on the new advances in this area Table 2. Contact lens problem with loading is resolved when the loaded drug is formulated as NP and at the same time the delivery of NP is enhanced because the contact lens act as reservoir (98,99).

Drug	NP type	Improvement	Ref.
Timolol	Gold NP	enhance the uptake of the drug into the CL by soaking method	(100)
triamcinolone acetonide	nanosuspension	Significant increase in loading capacity of the lens from the nanosuspension compared to solution	(101)
Phomopsidione	NP	Reduce risk of bacterial infection associated with wearing CL, 99% of the microorganism growth was halted due to coating of the CL with NP	(102)
Ketotifen	Silica shell NP	The NP laden CL extended the release of the drug for 10 days	(103)
Silver	NP	Reduce risk of bacterial infection associated with wearing CL. Excellent antibacterial activity was observed	(104)
dimyristoyl phosphatidylcholine	Liposomes	The liposme laden CL extend the release of the drug for 8 days	(105)
Resina Draconis	Solid lipid nanoparticles	Increase PCRT and higher permeability of the drug	(106)
Timolol	NP	The release of the loaded CL was extended to one month	(107)
Prednisolone	Nanocapsule	Improve PCRT and loading efficiency of the CL	(108)
prednisolone	NP	The release of the drug was sustained when the NP incorporated into CL. The relase of the drug was 10.8 % from the CL compared to 42.3% of NP in 24 h	(109)
Natamycin	NP	The loading of the drug into the CL was improved and the release was sustained up to 12 h	(110)
loteprednol etabonate	NP	The release of the drug was extended to 12 days	(111)
Dysprosium	NP Nanorods Nanocomposites	The CL used as delivery medium for the three types of nanoformulation.	(112)

Conclusion

Ocular inserts is a type of dosage form that have many advantages in ocular drug delivery and has been widely investigated and some are already available in the market. Their main advantages includes reduce instillation time, reduce use of preservatives, enhance bioavailability and enhance pateint complience. They can be prepared in different shapes and sizes which made them verstile. They can also incorporate different techniques with their formulation such as using vesicular systems and nanotechnology. However, their main disadvantages is cost and difficult to reproduce and the problem of converting to large scale production. Inspite of that they are promising dosage forms and their ability to incorporate different techniques made them intersting for formulation scientists.

References

1- JO& CUNHA-VAZ. The Blood-Ocular Barriers. Surv Ophthalmol. 1979;23(5):279–96.
2- Cholkar K, Patel SP, Vadlapudi AD, Mitra AK. Novel Strategies for Anterior Segment Ocular Drug Delivery. J Ocul Pharmacol Ther. 2013;29(2):106–23.
3- Ashaben Patel, Kishore Cholkar, Vibhuti Agrahari and AKM. Ocular drug delivery systems: An overview. World J

Pharmacol. 2015;2(2):47–64.
4- Bachu RD, Chowdhury P, Al-saedi ZHF, Karla PK, Boddu SHS. Ocular Drug Delivery Barriers — Role of Nanocarriers in the Treatment of Anterior Segment Ocular Diseases. Pharmaceutics. 2018;10(28):1–31.
5- Molokhia SA, Thomas SC, Garff KJ, Mandell KJ, Wirostko BM. Anterior Eye Segment Drug Delivery Systems : Current Treatments and Future Challenges. J Ocul Pharmacol Ther. 2013;29(2):92–105.
6- Gaudana R, Ananthula HK, Parenky A, Mitra AK. Ocular Drug Delivery. Am Assoc Pharm Sci. 2010;12(3):348–60.
7- Chen H, Jin Y, Sun L, Li X, Nan K, Liu H,. Recent Developments in Ophthalmic Drug Delivery Systems for Therapy of Both Anterior and Posterior Segment Diseases. Colloid Interface Sci Commun. 2018;24:54–61.
8- Burns E, Mulley GP. Practical Problems with Eye-drops Among Elderly Ophthalmology Outpatients. Age aging. 1992;21:168–70.
9- Taylor SA, Galbraith SM, Mills RP. Causes Of Non-Compliance With Drug Regimens In Glaucoma Patients : A Qualitative Study. J Ocul Pharmacol Ther. 2002;18(5):401–9.
10- Baudouin C, Labbé A, Liang H, Pauly A. Progress in Retinal and Eye Research Preservatives in eyedrops : The good , the bad and the ugly q. Prog Retin Eye Res.34–312:(4)29;2010 .: http://dx.doi.org/10.1016/j.preteyeres.2010.03.001
11- Ali FM, Al-shohani AD. Preparation and Evaluation of in situ Ophthalmic Gel with a Dual Triggered Mechanism for the Delivery of Gatifloxacin and Betamethasone. A-Rafidain J Med Sci. 2024;6(2):56–63.
12- Ding D, Kundukad B, Somasundar A, Vijayan S, Khan SA, Doyle PS. Design of Mucoadhesive PLGA Microparticles for Ocular Drug Delivery. ACS Appl Bio Mater. 2018;1:561–71.
13- Humberto J, Daza U, Righetto GM, Chaud MV, Conceic V. PVA / anionic collagen membranes as drug carriers of ciprofloxacin hydrochloride with sustained antibacterial activity and potential use in the treatment of ulcerative keratitis. J Biomater Appl. 2020;35(3):1–12.
14- Shi H, Wang Y, Bao Z, Lin D, Liu H, Yu A,. Thermosensitive glycol chitosan-based hydrogel as a topical ocular drug delivery system for enhanced ocular bioavailability. Int J Pharm. 2019;570(June):1–7.
15- Göttel B, Martins J, Souza D, De CS, Syrowatka F, Fiorentzis M,. Electrospun nanofibers- a promising solid in-situ gelling alternative for ocular drug delivery. Eur J Pharm Biopharm . 146;2020(January):125–32.: https://doi.org/10.1016/j.ejpb.2019.11.012
16- ahmed Khames; Mohammad a Khaleel; Mohamed F el-Badawy; ahmed Oh el-Nezhawy. Natamycin solid lipid nanoparticles – sustained ocular delivery system of higher corneal penetration against deep fungal keratitis : preparation and optimization. Int J Nanomedicine. 2019;14:2515–31.
17- Huang J, Peng T, Li Y, Zhan Z, Zeng Y, Huang Y,. Ocular Cubosome Drug Delivery System for Timolol Maleate : Preparation , Characterization , Cytotoxicity , Ex Vivo , and In Vivo Evaluation. AAPS PharmSciTech. 2017;18(November):2919–2926.
18- Wei Y, Hu Y, Shen X, Zhang X, Guan J, Mao S. Design of circular-ring film embedded contact lens for improved compatibility and sustained ocular drug

delivery. Eur J Pharm Biopharm . 157;2020(May):28–37.: https://doi.org/10.1016/j.ejpb.2020.09.010

19- Bertens CJF, Martino C, Osch MC Van, Lataster A, Dias AJAA, Biggelaar FJHM Van Den,. Design of the ocular coil , a new device for non-invasive drug delivery. Eur J Pharm Biopharm . .30–150:120;2020: https://doi.org/10.1016/j.ejpb.2020.03.010

20- Land DL, Benjamin WJ. Sizes and Shapes of Conjunctiva1 Inserts. ICLC. 1994;21(November):212–7.

21- Grassiri B, Zambito Y, Bernkop-schnürch A. Strategies to prolong the residence time of drug delivery systems on ocular surface. Adv Colloid Interface Sci. 2021;288:1–16.

22- Article R. Ocuserts : A Novel Formulation Approach in Drug Delivery System. Saudi J Med Pharm Sci. 2020;4929:420–5.

23- Gupta CCBSJPK. Intracanalicular Insert in the Management of Ocular In flammation and Pain Following Ophthalmic Surgery : Design , Development and Place in Therapy. Clin Ophthalmol. 2020;14:89–94.

24- Maichuk Y. Ophthalmic drug inserts. Invest Ophthalmol Vis Sci. 1975;(February):87–90.

25- RICHARD BENS- INGER, DONG H. SHIN, MICHAEL A. KASS, STEVEN M. PODOS ABB. Pilocarpine ocular inserts. Invest Ophthalmol Vis Sci. 1976;(December):1008–10.

26- PEI- KEI LEE, YEONC-TAI SHEN AME. The long-acting Ocusert-pilocarpine system in the management of glaucoma. Invest Ophthalmol Vis Sci. 1975;14(1):43–6.

27- Macoul KL, Pavan-langston D. Pilocarpine Ocusert System for Sustained Control of Ocular Hypertension. Arch Ophthalmol. 1975;93:587–90.

28- Bloomfield SE, Dunn MW, Miyata T, Randle SS, Rubin AL, Kurt H. Soluble Artificial Tear Inserts. Arch Ophthalmol. 1977;95:247–50.

29- Mirzaeei S, Taghe S, Alany RG, Ali N. Eudragit® L100/Polyvinyl Alcohol Nanoparticles Impregnated Mucoadhesive Films as Ocular Inserts for Controlled Delivery of Erythromycin: Development, Characterization and In Vivo Evaluation. Biomedicines. 2022;10(1917):1–19.

30- U. Finne VW and AU. Modification of ocular and systemic absorption of timolol from ocular inserts by a buffering agent and a vasoconstrictor. Int J Pharm. 1990;65:19–27.

31- Hosaka S, Ozawa H, Tanzawa H, Nichols RL. In vivo evaluation of ocular inserts of hydrogel impregnated with antibiotics for trachoma therapy. Biomaterials. 1983;4:243–8.

32- Hitoshi Ozaw;z, Shuntaro Hosaka TK and HT. Ocular inserts for controlled release of. Biomaterials. 1983;4:170–4.

33- Wright P, Vogel R. Slow-release artificial tear inserts in the treatment of dry eyes resulting from the oculomucocutaneous syndrome. Br J ofOphthalmology,. 1983;67:393–7.

34- Qureshi J, Hussain F, Ijaz H, Afzal M. Fabrication and evaluation of Olopatadine hydrochloride ocular inserts. J Plast Film Sheeting. 2020;36(3):1–17.

35- Gevariya HB, Jayvadan P. Sustained ophthalmic delivery of levofloxacin from once a day ocuserts. Int J Pharm Pharm Sci. 2009;1(Suppl. 1):24–23.

36- M PCR, Nappinnai M, Raju S, V UMR, Reddy B. Fluconazole Ocular Inserts : Formulation and In -Vitro Evaluation. J

Pharm Sci Res. 2010;2(6):2010.
37- Sultana Y, Aqil M, Ali A. Ocular inserts for controlled delivery of pefloxacin mesylate : Preparation and evaluation. Acta Pharma. 2005;55:305–14.
38- Karthikeyan D, Bhowmick M, Pandey VP, Nandhakumar J, Sengottuvelu S, Sonkar S,. The concept of ocular inserts as drug delivery systems : An overview. Asian J Pharm. 2008;(December):192–200.
39- Lp J. A Summary of Recent Advances in Ocular Inserts and Implants. J Bioequiv Availab. 2017;9(1):320–3.
40- Noori MM, Al-shohani ADHH, Yousif NZ. Fabrication and characterization of new combination ocular insert for the combined delivery of tinidazole and levofloxacin. Mater Today Proc . 80;2023(Part 3):2652–9.: https://doi.org/10.1016/j.matpr.2021.07.008
41- Dhaka M, Mazumdar R, Haque R. Preparation and assessment of ocular inserts containing sulbactum for controlled drug delivery. J Drug Deliv Ther. 2020;10(1-s):66–71.
42- Kriti D, Yashika U. Ocular inserts : Novel approach for drug delivery into eyes. GSC Biol Pharm Sci. 2019;07(03):1–7.
43- Nisar S, Shah H, Nawaz A, Javed H, Rafiq M, Riaz R,. Preparation and In Vitro / In Vivo Evaluation of Antihistaminic Ocular Inserts. Pharm Chem J. 2018;52(7):588–95.
44- P. I. PUNCH, D. H. SLATTER NDC 8c MEE. Investigation of gelatin as a possible biodegradable matrix for sustained delivery of gentamicin to the bovine eye. J veterenary Pharmacol Ther. 1985;8(3):335–8.
45- CJ., Heller. Controlled release of biologically active compounds from bioerodible polymers. Biomaterials. 1980;1(January):51–7.
46- Beena K. Ocular drug delivery system : Approaches to improve ocular bioavailability. GSC Biol Pharm Sci. 2019;06(03):1–10.
47- Mirzaeei S, Alizadeh M. Design and Evaluation of Soluble Ocular Insert For Controlled Release of Chloramphenicol. J reports Pharm Sci. 2017;6(2):123–33.
48- Tatke A, Dudhipala N, Janga KY, Soneta B. Melt-Cast Films Significantly Enhance Triamcinolone Acetonide Delivery to the Deeper Ocular Tissues. Pharmaceutics. 2019;11(158):1–14.
49- Deborah Pavan-Langston, MD; Roger H.S. Langston MPAG. Idoxuridine Ocular Insert Therapy Use in Treatment of Experimental Herpes Simplex Keratitis Deborah. Ann Ophthalmol. 1975;93(December):1349–51.
50- Bloomfield SE, Miyata T, Dunn MW, Bueser N, Stenzel KH, Rubin AL. Soluble Gentamicin Ophthalmic Inserts as a Drug Delivery System. Arch Ophthalmol. 1978;96(May):885–7.
51- Patil SS, Bade A, Tagalpallewar A. Design, optimization and pharmacodynamic comparison of dorzolamide hydrochloride soluble ocular drug insert prepared by using 32 factorial design. J Drug Deliv Sci Technol46;2018 .(August):138–47.: https://doi.org/10.1016/j.jddst.2018.05.010
52- Kendre PN, Kadam PD, Jain SP, Vibhute SK, Pote AK, Kendre PN,. Design , fabrication , and characterization of graft co-polymer assisted ocular insert : a state of art in reducing post-operative pain. Drug Dev Ind Pharm–1:(12)46;2020 . .12: https://doi.org/10.1080/03639045.2020.1833908
53- 53. Sebastián-morelló M, Calatayud-pascual MA, Rodilla V. Ex

vivo rabbit cornea diffusion studies with a soluble insert of moxifloxacin. Drug Deliv Transl Res. 2017;(November):1–8.

54- Terreni E, Burgalassi S, Chetoni P, Tampucci S, Zucchetti E, Fais R,. Development and Characterization of a Novel Peptide-Loaded Antimicrobial Ocular Insert. Biomolecules. 2020;10:1–17.

55- Abdelkader H, Wertheim D, Pierscionek B, Alany RG. Curcumin In Situ Gelling Polymeric Insert with Enhanced Ocular Performance. Pharmaceutics. 2020;12(12):1–17.

56- E. Sravanthi Reddy1 , Himansu Bhusan Samal1 SAS. Design and Characterization of Ofloxacin and Dexamethasone Ocular Inserts Using Combination of Hydrophobic and Hydrophilic Polymers. Asian J Pharm. 2017;11(1):S62–8.

57- Aburahma MH, Mahmoud AA. Biodegradable Ocular Inserts for Sustained Delivery of Brimonidine Tartarate : Preparation and In Vitro / In Vivo Evaluation. AAPS PharmSciTech. 2011;12(4):1335–47.

58- MAJUMDAR PKPRKDK. Design and evaluation of moxifloxacin hydrochloride ocular inserts. Acta Pharm. 2012;62:93–104.

59- Valarmathi S, Shanmugam S, Kumar SS, Shanmugasundaram P. In Vivo studies of Ophthalmic Ocular Insert Containing Aciclovir. Res J Pharm Technol. 2017;10(7):2139–42.

60- Dawaba HM, Dawaba AM. Development and evaluation of extended release ciprofloxacin HCl ocular inserts employing natural and synthetic film forming agents. J Pharm Investig . .257–49:245;2019: http://dx.doi.org/10.1007/s40005-018-0400-x

61- Luchs JI, Nelinson DS, Macy JI. Efficacy of Hydroxypropyl Cellulose Ophthalmic Inserts (LACRISERT) in Subsets of Patients With Dry Eye Syndrome : Findings From a Patient Registry. Cornea. 2010;29(12):1417–27.

62- Mcdonald M, Aversa GD, Perry HD, Wittpenn JR, Donnenfeld ED. Hydroxypropyl cellulose ophthalmic inserts (lacrisert) reduce the signs and symptoms of dry eye syndrome and improve patient quality of life. Trans Am Ophthalmol Soc. 2009;107:214–22.

63- Lee A, Blair HA. Dexamethasone Intracanalicular Insert : A Review in Treating Post - Surgical Ocular Pain and Inflammation. Drugs–80:1101;2020 . .1108: https://doi.org/10.1007/s40265-020-01344-6

64- Sabri ZY, Al-shohani ADHH. The Effect of Molecular Imprinting on the Loading and Release of Poorly Water Soluble Drug in Hydrogel Contact Lenses. Iraqi J Pharm Sci. 2023;32(1):139–46.

65- Khan S, Ali A, Singhavi D, Yeole P. Controlled Ocular Delivery of Acyclovir through Rate Controlling Ocular Insert of Eudragit : A Technical Note. AAPS PharmSciTech. 2008;9(1):169–73.

66- Harry A. Quigley, MD; Irvin P. Pollack, MD; Thomas S. Harbin, Jr. MF. Pilocarpine Ocuserts:Long-Term Clinical Trials and Selected Pharmacodynamics. Arch Ophthalmol. 1975;93(9):771–5.

67- Desai AR, Maulvi FA, Desai DM, Shukla MR, Ranch KM, Vyas BA,. Multiple drug delivery from the drug-implants-laden silicone contact lens : Addressing the issue of burst drug release. Mater Sci Eng C . 112;2020(March):1–13.: https://doi.org/10.1016/j.msec.2020.110885

68- Choi SW, Kim J. Therapeutic Contact

Lenses with Polymeric Vehicles for Ocular Drug Delivery : A Review. Materials (Basel). 2018;11:1–20.

69- Maulvi FA, Shaikh AA, Lakdawala DH, Desai AR, Pandya MM, Singhania SS,. Design and optimization of a novel implantation technology in contact lenses for the treatment of dry eye syndrome : In vitro and in vivo evaluation. Acta Biomater . .21–53:211;2017: http://dx.doi.org/10.1016/j.actbio.2017.01.063

70- Kusrini E, Hashim F, Abdullah A, Putra N. Design , synthesis and antiamoebic activity of dysprosium-based nanoparticles using contact lenses as carriers against Acanthamoeba sp . Acta Ophthalmol. 2021;99(2):e178–88.

71- Silva D, Sousa HC De, Helena M, Santos LF, Salema M, Alvarez-lorenzo C,. Moxifloxacin-imprinted silicone-based hydrogels as contact lens materials for extended drug release. Eur J Pharm Sci . .11–156:1;2021: https://doi.org/10.1016/j.ejps.2020.105591

72- 72. Maulvi FA, Parmar RJ, Desai AR, Desai DM, Shukla MR, Ranch KM,. Tailored gatifloxacin Pluronic ® F-68-loaded contact lens : Addressing the issue of transmittance and swelling. Int J Pharm. 2020;581(May):1–9.

73- Xu B, Liu T. Journal of Drug Delivery Science and Technology Travoprost loaded microemulsion soaked contact lenses : Improved drug uptake , release kinetics and physical properties. J Drug Deliv Sci Technol57;2020 .(May):1–6.: https://doi.org/10.1016/j.jddst.2020.101792

74- Prima G Di, Licciardi M, Pavia FC, Ignazio A, Monte L, Cavallaro G,. Microfibrillar polymeric ocular inserts for triamcinolone acetonide delivery. Int J Pharm567;2019 .(April):1–13.: https://doi.org/10.1016/j.ijpharm.2019.118459

75- Mohammadsadeghi A, Farjadian F, Alipour S. Sustained release of linezolid in ocular insert based on lipophilic modified structure of sodium alginate. Iran J Basic Med Sci. 2021;24(3):331–40.

76- Wafa HG, Essa, Ebtessam A AEE-S& GMEM. Ocular films versus film-forming liquid systems for enhanced ocular drug delivery. Drug Deliv Transl Res. 2020;29(July):1–12.

77- Aher ND, Nair HA. Bilayered Films Based on Novel Polymer Derivative for Improved Ocular Therapy of Gatifloxacin. Sci World J. 2014;(January):1–9.

78- Hasan TI, Ahmed AA. Characterization, antibacterial and antibiofilm evaluation of biosynthesized silver nanoparticles from Pseudomonas aeruginosa against drug resistant Acinetobacter baumannii. Al Mustansiriyah J Pharm Sci. 2023;23(3):307–21.

79- Ghareeb MM, Mohammed MS. TOPICAL NANOEMULSION-BASED GEL OF ISOCONAZOLE NITRATE. Al Mustansiriyah J Pharm Sci. 2023;23(4):378–96.

80- Khiev D, Mohamed ZA, Vichare R, Paulson R, Bhatia S, Mohapatra S,. Emerging Nano-Formulations and Nanomedicines Applications for Ocular Drug Delivery. Nanomaterials. 2021;11(173):1–18.

81- Shrivastava M, Kumar K, Author C. Formulation and Characterization of Eudragit RS 100 Nanosuspension for Ocular Delivery of Indomethacin. Int J Res Pharma Pharm Sci. 2020;1(2):11–28.

82- Merve U, Yenilmez E. Olopatadine hydrochloride loaded Kollidon ® SR

nanoparticles for ocular delivery : Nanosuspension formulation and in vitro – in vivo evaluation. J Drug Deliv Sci Technol51;2019 .(March):506–12.: https://doi.org/10.1016/j.jddst.2019.03.016

83- Grimaudo MA, Amato G, Carbone C, Diaz-rodriguez P, Musumeci T, Concheiro A,. Micelle-nanogel platform for ferulic acid ocular delivery. Int J Phar576;2020 .(December 2019):1–9.: https://doi.org/10.1016/j.ijpharm.2019.118986

84- Dong P, Rakesh KP, Manukumar HM, Hussein Y, Mohammed E. Innovative nano-carriers in anticancer drug delivery-a comprehensive review. Bioorg Chem85;2019 .(January):325–36.: https://doi.org/10.1016/j.bioorg.2019.01.019

85- Thakkar S, Misra M. Electrospun polymeric nanofibers: New horizons in drug delivery Shreya. Eur J Pharm Sci . 107;2017(September):148–67.: http://dx.doi.org/10.1016/j.ejps.2017.07.001

86- Zaarour B, Zhu L, Jin X. A Review on the Secondary Surface Morphology of Electrospun Nanofibers : Formation Mechanisms , Characterizations , and Applications. Chem Sel. 2020;5:1335–48.

87- Ibrahim HM, Klingner A. A review on electrospun polymeric nanofibers : Production parameters and potential applications. Polym Test . 90;2020(October):1–18.: https://doi.org/10.1016/j.polymertesting.2020.106647

88- Zelkó SO and R. A Systematic Review of Drug-Loaded Electrospun Nanofiber-Based Ophthalmic Inserts. Pharmaceutics. 2021;13(1637):2–22.

89- 89. Mirzaeei S, Berenjian K, Khazaei R. Preparation of the Potential Ocular Inserts by Electrospinning Method to Achieve the Prolong Release Profile of Triamcinolone Acetonide. Tabriz Univ Med Sci.7–21:(1)8;2018 .: https://doi.org/10.15171/apb.2018.003

90- Polat HK, Pehlivan SB, Özkul C, Çalamak S, Aytekin E, Fırat A,. Development of Besifloxacin HCl Loaded Nanofibrous Ocular Inserts for the Treatment of Bacterial Keratitis: In Vitro, Ex Vivo and In Vivo Evaluation. Int J Pharm. 2020;585(30):119552.

91- Singla J, Bajaj T, Goyal AK, Rath G. Development of Nanofibrous Ocular Insert for Retinal Delivery of Development of Nanofibrous Ocular Insert for Retinal Delivery of Fluocinolone Acetonide. Curr Eye Res . 2018;(December):1–10.: https://doi.org/10.1080/02713683.2018.1563196

92- Khan I, Saeed K, Khan I. Nanoparticles : Properties , applications and toxicities. Arab J Chem.31–908:(7)12;2019 .: https://doi.org/10.1016/j.arabjc.2017.05.011

93- Mohammadi G, Mirzaeei S, Taghe S, Mohammadi P. Preparation and Evaluation of Eudragit ® L100 Nanoparticles Loaded Impregnated with KT Tromethamine Loaded PVA -HEC Insertions for Ophthalmic Drug Delivery. Adv Pharm Bull . .600–593:(4)9;2019: https://doi.org/10.15171/apb.2019.068

94- Morsi N, Ghorab D, Refai H, Teba H. Nanodispersion-loaded mucoadhesive polymeric inserts for prolonged treatment of post-operative ocular inflammation. J Microencapsul. 2017;34(3):280–92.

95- Khalil IA, Ali IH, El-sherbiny IM. Noninvasive biodegradable nanoparticles-in-nanofibers single-dose

ocular insert: in vitro, ex vivo and in vivo evaluation. Nanomedicine. 2019;14(1):33–55.

96- Neslihan Üstündağ-Okura, Evren Homan Gökçea, Duygu İnci Bozbıyıkb, Sait Eğrilmezc GE& ÖÖ. Novel nanostructured lipid carrier-based inserts for controlled ocular drug delivery : evaluation of corneal bioavailability and treatment efficacy in bacterial keratitis. Expert Opin Drug Deliv. 2015;(August):1–17.

97- Shukr MH. Novel in situ gelling ocular inserts for voriconazole-loaded niosomes : design , in vitro characterisation and in vivo evaluation of the ocular irritation and drug pharmacokinetics. J Microencapsul. 2016;33(1):71–9.

98- Thomas D. Pollard , Iria Seoane-Via˜no , Jun Jie Ong , Patricija Januskaite , Sahar Awwad , Mine Orlu , Manuel F. Bande , Abdul W. Basit AG. Inkjet drug printing onto contact lenses : Deposition optimisation and non-destructive dose verification. Int J Pharm. 2023;5(December):1–10.

99- Industries SP, Saha P. CONTACT LENSES : A DEVELOPMENT TOWARDS OCULAR DRUG DELIVERY World Journal of Pharmaceutical Research CONTACT LENSES : A DEVELOPMENT TOWARDS OCULAR DRUG. World J Pharm Res. 2017;6(9):207–16.

100- Maulvi FA, Patil RJ, Desai AR, Shukla MR, Vaidya RJ, Ranch KM,. Effect of gold nanoparticles on timolol uptake and its release kinetics from contact lenses : In vitro and in vivo evaluation. Acta Biomater . .62–86:350;2019: https://doi.org/10.1016/j.actbio.2019.01.004

101- Eva Garc´ıa-Millan, Monica Quint´ans-Carballo FJO-E. Improved release of triamcinolone acetonide from medicated soft contact lenses loaded with drug nanosuspensions. Int J Pharm . .36–226:(1)525;2017: http://dx.doi.org/10.1016/j.ijpharm.2017.03.082

102- Yuso M, Yenn W, Nee W, Ring C, Najib M, Misri B,. Phomopsidione nanoparticles coated contact lenses reduce microbial keratitis causing pathogens. Exp Eye Res. 2019;178(January):10–4.

103- Maulvi FA, Mangukiya MA, Patel PA, Vaidya RJ, Koli AR, Ranch KM,. Extended release of ketotifen from silica shell nanoparticle-laden hydrogel contact lenses : in vitro and in vivo evaluation. J Mater Sci Mater Med. 2016;27(113):1–13.

104- Sedigheh B, Bazzaz F, Khameneh B, Jalili-behabadi M, Malaekeh-nikouei B, Ahmad S. Preparation , characterization and antimicrobial study of a hydrogel (soft contact lens) material impregnated with silver nanoparticles. Contact Lens Anterior Eye.52–149:(3)37;2014 .: http://dx.doi.org/10.1016/j.clae.2013.09.008

105- Gulsen D, Li C, Chauhan A. Dispersion of DMPC Liposomes in Contact Lenses for Ophthalmic Drug Delivery. Curr Eye Res. 2005;30(12):1071–80.

106- Hao J, Wang X, Bi Y, Teng Y, Wang J, Li F,. Colloids and Surfaces B : Biointerfaces Fabrication of a composite system combining solid lipid nanoparticles and thermosensitive hydrogel for challenging ophthalmic drug delivery. Colloids Surfaces B Biointerfaces.20–114:111;2014 .: http://dx.doi.org/10.1016/j.colsurfb.2013.09.059

107- Jung H, Abou-jaoude M, Carbia BE,

Plummer C, Chauhan A. Glaucoma therapy by extended release of timolol from nanoparticle loaded silicone-hydrogel contact lenses. J Control Release.9–82:(1)165;2013 .: http://dx.doi.org/10.1016/j.jconrel.2012.10.010

108- T. Katzer1, P. S. Chaves1, A.R.Pohlmann2? 3, S.S.Guterres1? 3 and RCRB 3. Loading A Drug on Contact Lenses Using Polymeric Nanocapsules : Effects on Drug Release , Transparency , and Ion Permeability. J Nanosci Nanotechnol. 2017;17(12):9286–94.

109- Elshaer A, Mustafa S, Kasar M, Thapa S, Ghatora B. Nanoparticle-Laden Contact Lens for Controlled Ocular Delivery of Prednisolone : Formulation Optimization Using Statistical Experimental Design. Pharmaceutics. 2016;8(2):1–16.

110- Phan C, Subbaraman L, Liu S. In vitro uptake and release of natamycin Dex-b-PLA nanoparticles from model contact lens materials. J Biomater Sci ,polymer Ed. 2014;25(1):37–41.

111- Nasra FH, Khoee S, Mehdi M. Preparation and Evaluation of Contact Lenses Embedded with Polycaprolactone-based Nanoparticles , for Ocular Drug Delivery. Biomacromolecules. 2016;17(2):485–495.

112- Kusrini E, Sabira K, Hashim F, Abdullah NA, Usman A, Putra N,. Design , synthesis and antiamoebic activity of dysprosium-based nanoparticles using contact lenses as carriers against Acanthamoeba sp . Acta Ophthalmol. 2021;99(2):e178–88.