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Ophthalmic drug delivery by contact lenses

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ABSTRACT

There has been considerable interest in the potential application of contact lenses for ocular drug delivery. Static barriers (different layers of cornea, sclera and retina including blood aqueous and blood retinal barriers), dynamic barriers (chroidal and conjunctival blood flow) pose a significant challenge for delivery of a drug to the eye. Current ophthalmic drug delivery systems are insufficient, especially eye drops, which allow approximately 95% of the drug contained in the drops to be lost due to absorption through the conjunctiva or through the tear drainage. The present article shows that the use of contact lenses has been a method to deliver drugs to the eye in an efficient manner. Contact lenses are emerging as an alternative ophthalmic drug delivery system to resolve the shortcomings of the conventional / topical application methods like eye drops and ointments. The advantages of using contact lenses are in dosing regimen, bioavailability and prolonging the residence time of drugs .This article shows that the contact lenses are ideal choice for ophthalmic drug delivery. This review highlights the drug delivery through contact lens based ophthalmic drug delivery systems with significant potential to use in ocular therapeutics.

Keywords: Contact lens, ocular drugs, Barriers, ocular drug release

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INTRODUCTION

Eye is the window of our soul. The eye is unique organ from anatomical and physiological point of view. Without eye we can not enjoy the beauty of the nature. The eye has special attributes that allow local drug delivery and non – invasive clinical assessment of disease but also makes understanding disease pathogenesis and ophthalmic drug delivery challenges. Topical eye drops proves to be highly beneficial to the patients due to their persuade and economical effectiveness. But due to their poor absorption results in multiple dosing for wide periods to achieve therapeutic drug concentrations. Contact lenses are used to deliver an effective amount of drug to the eye with précised target dosing at a prolonged and elongated rate, to increase bioavailability of the drug. Several commercial ocular delivery devices are available in market. Contact lenses (CLs) turned out to be a satisfied drug delivery material for ophthalmic drug delivery system.

ADVANTAGES OF OCULAR DRUG DELIVERY SYSTEMS

- Increased accurate dosing. To overcome the side effects of pulsed dosing produced by conventional systems.
- To provide sustained and controlled drug delivery.
- To increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to corneal surface.
- To provide targeting within the ocular globe so as to prevent the loss to other ocular tissues.
- To circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.
- To provide comfort, better compliance to the patient and to improve therapeutic performance of drug.
- To provide better housing of delivery system.

HISTORY

The first successful contact lens (CL) material which has been used as early as in the 1930s was the Polymethyl methacrylate (PMMA) (1). Later the use of soft contact lens (SCL) for ophthalmic drug delivery was reported by Sedlacek in 1965 (2). The discovery of Hydrogels was done by Witcherle and Lim in the early 1960s, and they were used broadly(3) ,while in the 70s ,Kaufman et al played a major role for finding out the benefits of contact lens for ocular drug delivery (4). The use of Conventional Hydrogel (CH) contact lenses posses one major problem was that there was a lack of adequate oxygen transmission to the cornea, resulting in hypoxia related problems during overnight wear, restricting their long term therapeutic potential. In 1990s , the solution of this issue came as in the form of when highly oxygen permeable Silicone Hydrogel (SH) contact lenses were introduced. The use of these lenses permitted near normal corneal physiology during extended periods of wear and the concept for adopting of contact lenses for ocular drug delivery became more capable (5), but the main shortcoming of Silicone was poor wettability of the lens and the deposition of the lipid is rapid due to its hydrophobic nature (6). Contact lenses with optimal of hypoxic difficulties were also described by Covey et al (7).

ANATOMY AND PHYSIOLOGY OF EYE

The eye is the most precious organ with a wall consisting of three layers: the outer sclera, the middle chroid layer and the inner retina. The sclera is a tough fibrous coating that protects the inner layers. It is white except for the transparent area at the front, the cornea which allows light to enter the eye (8).

THE CHOROID LAYER

The choroid layer, situated inside the sclera containing many blood vessels and is modified at the front of the eye is the pigmented iris. The bioconvex lens is situated just behind the pupil. The chamber behind the lens is filled with vitreous humor, a gelatinous substance occupying 80% of the eye ball. The anterior and posterior chamber are situated between the cornea and iris, and iris and lens, respectively and filled with aqueous humor. At the back of the eye is the light detecting retina**.**

A. SCELERA

The sclera (white portion of the eye) is the tough white sheath that forms the outer – layer of the ball. It is a firm fibrous membrane that maintains the shape of the eye (9).

B. CONJUNCTIVA

The conjunctiva is a thin transparent mucous epithelial barrier, lines the inside of the eyelids and covers the anterior one-third of the eyeball. The respective portion of conjunctiva is referred to as the palpebral and bulbar conjunctiva. The conjunctiva is composed of two layers i.e,an outer epithelium and its underlying stroma (substantia propria). The exposed surface of the eye includes conjunctiva and cornea and is covered with the tear film.

C. CORNEA

The cornea is a strong clear bulge located at the front of the eye .Surface of the adult cornea has a radius of approximately 8mm.It is an important part of an eye as it refracts light entering the eye which then passes through the pupil and onto the lens (which then focuses the light onto the retina).Cornea does not contain any blood vessels. It is supplied by many nerves derived from the ciliary nerves. It is however extremely sensitive.

D. AQUEOUS HUMOR

It is a jelly- like substance located in the outer / front chamber of the eye. It is a watery fluid that fills the “anterior chamber of the eye” which is located immediately behind the cornea and in front of the lens. It is very slightly alkaline salt solution that includes tiny quantities of sodium and chloride ions. It is mainly produced by the ciliary processes. Aqueous humour consists of pressure dependent and pressure independent pathways. In human, the rate of aqueous turnover is approximately 1% -1.5% of the anterior chamber volume per minute (10).

E. PUPIL

It generally appears to be the “dark” centre of the eye. It can be more accurately described as the circular aperture in the centre of the iris through which light passes into the eye. The pupil size (and therefore the amount of light that enters into the eye)is regulated by the pupillary reflex (commonly known as “light reflex”).

F. IRIS

This can be said as a thin circular contractile curtain located in front of the lens but behind the cornea. It is a diaphragm of variable size whose function is to adjust the size of the pupil to regulate the amount of light admitted into the eye. It is the coloured part of the eye (shades may vary from person to person like blue, green, brown, grey).

G. CILIARY MUSCLE

It is a ring of striated smooth muscles in the eye's middle layer that controls accommodation for viewing objects at varying distances and controls the flow of aqueous humour into schlemm's canal. The muscle has parasympathetic and sympathatetic innervation. The curvature of the lens can be altered by the contraction and the relaxation of the ciliary muscle. This process can be illustrated as the balance existing at any time between two states i.e, Ciliary Muscle Relaxed (This enables the eye to focus on distant objects)and Ciliary Muscle Contracted (This enables the eye to focus on near objects).

H. LENS

The lens is a transparent structure enclosed in a thin transparent capsule. It is located behind the pupil of the eye and encircled by the ciliary muscles. It helps to refract light travelling through the eye (which first refracted by the cornea). The lens focuses light into an image on the retina. It is able to do this because the shape of the lens is changed according to the distance from the eye of the object, the person is seeing at. This adjustment of shape of the lens is called accommodation and is achieved by the contraction and relaxation of the ciliary muscles.

I. VITREOUS HUMOUR

This is also known as the vitreous body. Each eye of the human body occupies approximately 80% vitreous humour. The vitreous humour is a perfectly transparent thin jelly – like substance that fills the chamber behind the lens of the eye. It is an albuminous fluid enclosed in a delicate transparent membrane called the hyaloid membrane.

J. RETINA

It is located at the back of the human eye. The retina can be explained as the "screen" on which an image is formed by light that has passed into the eye via the cornea, aqueous humour, pupil , lens and finally the vitreous humour before reaching the retina. The function of the retina is not just to be the screen onto which an image may be formed but the information contained in that image can be collected and it is transmitted to the brain in a suitable form for use by the body. It contains photosensitive cells known as (rods and cones) and their associated nerve fibres convert the light they detect into the nerve impulses that are then sent onto the brain along the optic nerve.

K. MACULA

The centre of the retina is called the macula. It contains a high concentration of photoreceptor cells which convert light into nerve signals. Because of the high concentration of photoreceptors, we are able to see fine details such as newsprint with the macula. At the very center of the macula is the fovea, the site of our sharpest vision.

l. CHOROID

The choroid layer is located behind the retina and absorbs unused radiation and nourishes the outer portion of the retina. It is thin, highly vascular (i.e it contains blood vessels) membrane that is dark brown in colour and contains a pigment that absorbs excess light and so prevents blurred vision (due to too much light on the retina).The choroid has one of the highest blood flows in the body. The choroid is loosely attached to the inner surface of the sclera by the lamina fusa.

M. OPTIC NERVE

The optic nerve (a bundle of over 1 million nerve fibers) is responsible for transmitting nerve signals from the eye to the brain. These nerve signals contain information on an image for processing by the brain. The front surface of the optic nerve, which is visible on the retina, is called the optic disk.

ACCESSORY ORGANS OF THE EYE:

The eye is protected by several structures:

- Eyebrows
- Eyelids and eyelashes
- Lacrimal apparatus

Eyebrows can be described as the protective organ which protects our eyeball from sweat, dust and from any foreign bodies. Eyelids protects conjunctiva which protects the delicate cornea and front of the eye. The lacrimal glands secrete tears which is composed of water, mineral salts, antibiotics, lysozyme (a bactericidal enzyme).Immediately on instillation drainage of the eye drops will take place through nasolacrimal system into gastrointestinal tract. The main cause of this can be like volume of fluid in peripheral tissue to exceed the normal lacrimal volume .When eye drops are administered, they are placed in lower conjunctiva sac. Apart from other layers of the eye these organs play a vital role for protection of the most sensitive, delicate and the most important organ of our body (11).

Contact lenses are thin and curved shape plastic discs which are made to cover the cornea (11). After application, contact lens adheres to the film of tears over the cornea due to the surface tension. Drug loaded contact lens have been designed for ocular delivery of numerous drugs such as beta – blockers, antihistamines and antimicrobials. It has been studied that in presence of contact lens, drug molecules have longer residence time in the post – lens tear film which ultimately lead to higher drug flux through cornea with less drug inflow into the nasolacrimal duct. Usually, drug is loaded into contact lens by soaking them in drug solutions. These soaked contact lenses demonstrated higher efficiency in delivering drug compared to conventional eye drops.

ADVANTAGES OF USING CONTACT LENSES

Eye drops are the most frequently used method of delivering drug to the eye, accounting for approximately 90% of all ophthalmic formulations (13).While eye drops are comfortable to instil but the low bioavailability of less than 5% is a major drawback. Contact lenses are favourably the most successful biomaterial currently available worldwide (17, 18).They has already been demonstrated to successfully correct refractive errors in patients. The addition of drug delivery can potentially increase the quality of life in patients by reducing dosing frequency. There is some evidence that concurrent contact lens and topical ophthalmic treatment is more effective than topical treatment alone (19).

The drugs released from the contact lens potentially have a prolonged contact time with the cornea leading to improved bioavailability (20). Over 50% of the drugs released from a contact lens can diffuse into the cornea, which at least 35 times more efficient than eye drops. This increase in efficiency permits substantially reduced concentrations to be used , decreasing the potential for side effects as less drug is absorbed systematically(21,22).
Another advantage for using a contact lens as a drug delivery platform is the ability to deliver drugs over extended time periods, which eliminates the need for multiple dosing. For ocular infections such as microbial keratitis, eye drop instillation can be as frequent as application every hour. This can be very difficult for patients especially during sleep and severe infections often lead to hospitilisation, purely to ensure appropriate drug administration. Contact lenses effectively serve as a drug reservoir and release the drug over a set time period. In an ideal situation, the target drug forms an interaction with the contact lens polymer , and dissociates from the lens network in a time dependent manner into the post – lens tear film for eventual absorption by the ocular tissues.

ROUTES OF OCULAR DRUG DELIVERY

There are several possible routes of drug delivery into the ocular tissues .The selection of the route of administration depends primarily on the target tissue .They are as follows,

TOPICAL ROUTE

Topical ocular drug administration is accomplished by eye drops but they have only a short contact time on the eye surface. The contact and thereby duration of drug action can be prolonged by formulation design(21).

SUBCONJUNCTIVAL ADMINISTRATION

Subconjuctival injections have been used to deliver drugs at increased levels to the uvea. Recently this mode of drug delivery has gained new speed for various reasons. The progress in materials sciences and pharmaceutical formulations have provided new enticing possibilities to develop controlled release formulations to deliver drugs to the posterior segment and to help in the healing process after surgery (21).

INTRAVITREAL ADMINISTRATION

Direct drug administration into the vitreous offers distinct advantage of more straightforward access to the vitreous and retina. It is important to note that delivery from the vitreous to the choroid is more complicated due to the hindrance by the RPE (Retinal Pigment Epithelium) barrier .Molecules of smaller size are able to diffuse rapidly in the vitreous but the mobility of molecules of larger size particularly positively charged is restricted(21).

OPTHALMIC DISORDERS

Conditions treated by the topical application of drugs include are as follows (22) :

- Conjunctivitis – an inflammation of the conjunctiva that may be caused by bacterial and viral infection, pollen and other allergens ,smoke and pollutants .
- Dry eye syndrome –the inadequate wetting of the ocular surface.
- Glaucoma – the build up of pressure in the anterior and posterior chambers of the choroid layer that occurs when the aqueous humour fails to drain properly.
- Iritis (anterior uveitis) – commonly has an acute onset with the patient suffering pain and inflammation of the eye.
- Keratitis – an inflammation of the cornea caused by bacterial, viral or fungal infections.
- Other conditions include the ophthalmic complications of Rosacea, Blepharitis (inflammation of the lid margins) and Chalazia (Meibomian cysts of the eyelid).

Drugs administered topically to the eye

It is known that most of the ophthalmic drugs contain functional groups such as alcohol , carboxylic acid and phenol , which lend themselves to simple derivatisation. Prodrugs (pharmacologically not active derivatives of drugs that are chemically or enzymatically converted to their active parent compound after administration) of pilocarpine and b- blocker have been used to enhance bioavailability.

MATERIALS FOR CONTACT LENSES

Many researchers have contributed many advantages to the use of hydrogel in contact lenses such as good transmission of visible light , high chemical and mechanical stability, affordable cost and high oxygen transmissibility(23).Poly –HEMA has a water content of about 38% , however, by applying other monomers such as methacrylic acid (MAA) with HEMA ,soft contact lenses (SCLs) with different water contents , hardness ,strength and oxygen permeabilities can be created. The role of HEMA and Aacrylic acid (AA) in contact lens based ophthalmic drug delivery system has also been published by other authors (24).

BARRIERS FOR OCULAR DELIVERY:

- DRUG LOSS FROM THE OCULAR SURFACE

After instillation, instilled substances are removed from the eye surface by the flow of lacrimal fluid. Even though the lacrimal turnover rate is only about 1micro litre / min the excess volume of the instilled fluid is flown to the nasolacrimal duct rapidly in a couple of minutes. Another source of non-productive drug removal is its systemic absorption instead of ocular absorption. Directly from the conjunctival sac systemic absorption may take place via local blood capillaries or after the flow of the solution to the nasal cavity (25).

- LACRIMAL FLUID-EYE BARRIERS

Drug absorption from the lacrimal fluid into the eye is limited by the corneal epithelium. Paracellular drug permeation is limited by the tight junctions formed by the corneal epithelial cells. Therefore, lipophilic drugs have typically at least an order of magnitude higher permeability in the cornea than the hydrophilic drugs. In general, the conjunctiva is leakier epithelium than the cornea and as compared to cornea its surface area is 20 times greater than cornea (25).

- BLOOD –OCULAR BARRIERS

Blood - ocular barriers protect the eye from the xenobiotics present in the blood stream. The barriers consist of two parts: blood aqueous barrier and blood –retina barrier. The anterior blood –eye barrier is composed of the endothelial cells in the uveam (beneath the sclera the middle layer of the eye .It consists of the iris ,ciliary body , and choroid).The access of plasma albumin into the aqueous humour is prevented by this barrier and this barrier also limits the access of hydrophilic drugs from plasma into the aqueous humour. The posterior barrier between blood stream and eye is comprised of retinal pigment epithelium (RPE) and the tight walls of the retinal capillaries. Unlike retinal capillaries the vasculature of the choroid has extensive blood flow and leaky walls. Drugs easily gain access to the choroidal extravascular space, but thereafter RPE and retinal endothelia limits the distribution of drug into the retina (25)

MECHANISM OF DRUG RELEASE

It has been penned down that the hydrophobic interactions of the active agents (i.e , drugs or other compounds) with the contact lens material is the most important factor in the adsorption and subsequent release of these compounds(26). Initially , material in the form of a cation or an anion in the soft contact lens forms an ionic complex with the drug content in the drug solution. After that applying the soft contact lens to the eye , ionic components in the tear fluid , such as Sodium ,Chlorine or other elements are replaced gradually with the drug contents. Continuously sustained release of drug takes place from the soft contact lens(27).Hydrogels are glassy in their dehydrated state , and the release of the drug generally involves simultaneous absorption of water and desorption of drug via a swelling controlled mechanism. The rate controlling factor responsible for the drug delivery is the resistance of the polymer to an increase in volume and change in shape(28).Soft contact lenses hence enables greater penetration of drug into the eye and also greater penetration of drug into the eye can be achieved with higher water content lenses(29).

TECHNIQUES FOR CONTACT LENS BASED DRUG DELIVERY SYSTEM

For extended and targeted drug delivery to cornea ,contact lenses can be the ideal choice. Release of ophthalmic drugs from commercial contact lenses is for only 1 – 2 hours(30)(36).The most convenient way to incorporate a drug into soft contact lenses is to soak preformed lenses in the drug solution(31)(37).Conventional soft contact lenses have the ability to absorb a number of drugs when the lenses are pre-soaked in the drug solution(32)(38),subsequently releasing them into the post lens lacrimal fluid. Antibiotics ,anti inflammatories and antiallergy agents have all been tested for their release into the ocular tissue , and while differences in the absolute

amount of the drug being released between commercial types of lens are seen ,the release time typically is limited to one or two hours. Contact lens containing silicone released less drug than the p-HEMA containing materials(33)(39).Given this restriction, increasing the duration of release of drug through use of colloidal system , molecular imprinting ,drug binding to the polymer, barriers dispersion ,sandwiching a PLGA (poly {lactic –co – glycolic acid })layer in a lens and developing novel materials has been advocated(34,35,40).

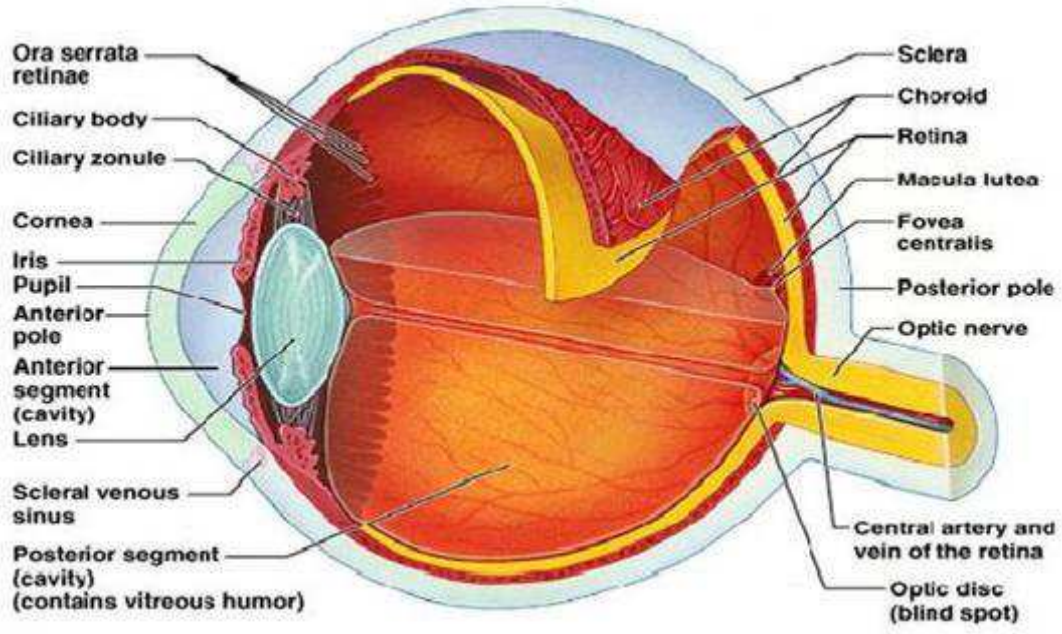

Fig 1 : Structure of eye

BENEFITS OF DRUG DELIVERY THROUGH CONTACT LENSES

- Diseases of eye like Glaucoma and dry eyes can be treated by using contact lenses which initiates sustained release of drugs to the eye.
- Lenses can be fabricated for the correction of vision ,then modification of eye colour or treatment of diabetic eye diseases can be achieved by the use of lens.
- Any sort of corneal wound healing can also be achieved by the use of contact lenses.

COMMERCIALLY AVAILABLE CONTACT LENSES

- Soft contact lenses (Silicone hydrogel and acrylate hydrogel)
- Silicone hydrogel materials were balafilcon A (PureVision ,Bausch and Lomb)
- Comfilcon A (Biofinity,CooperVision)
- Galyfilcon A (Acuvue Advance ,Johnson and Johnson)
- Lotrafilcon A(Night and Day ,CIBA Vision)
- Lotrafilcon B (CIBA Vision)
- Senofilcon A (Acuvue Oasys ,Johnson and Johnson)

Conventional lens material are as follows:

- Alphafilcon A (Soft lens 66 , Bausch and Lomb)
- Etafilcon A (Acuvue 2 ,Johnson and Johnson)
- Polymacon (Softlens 38,Bausch and Lomb)

Silicone hydrogel materials

Balafilcon A – Delivers highest amount of drug

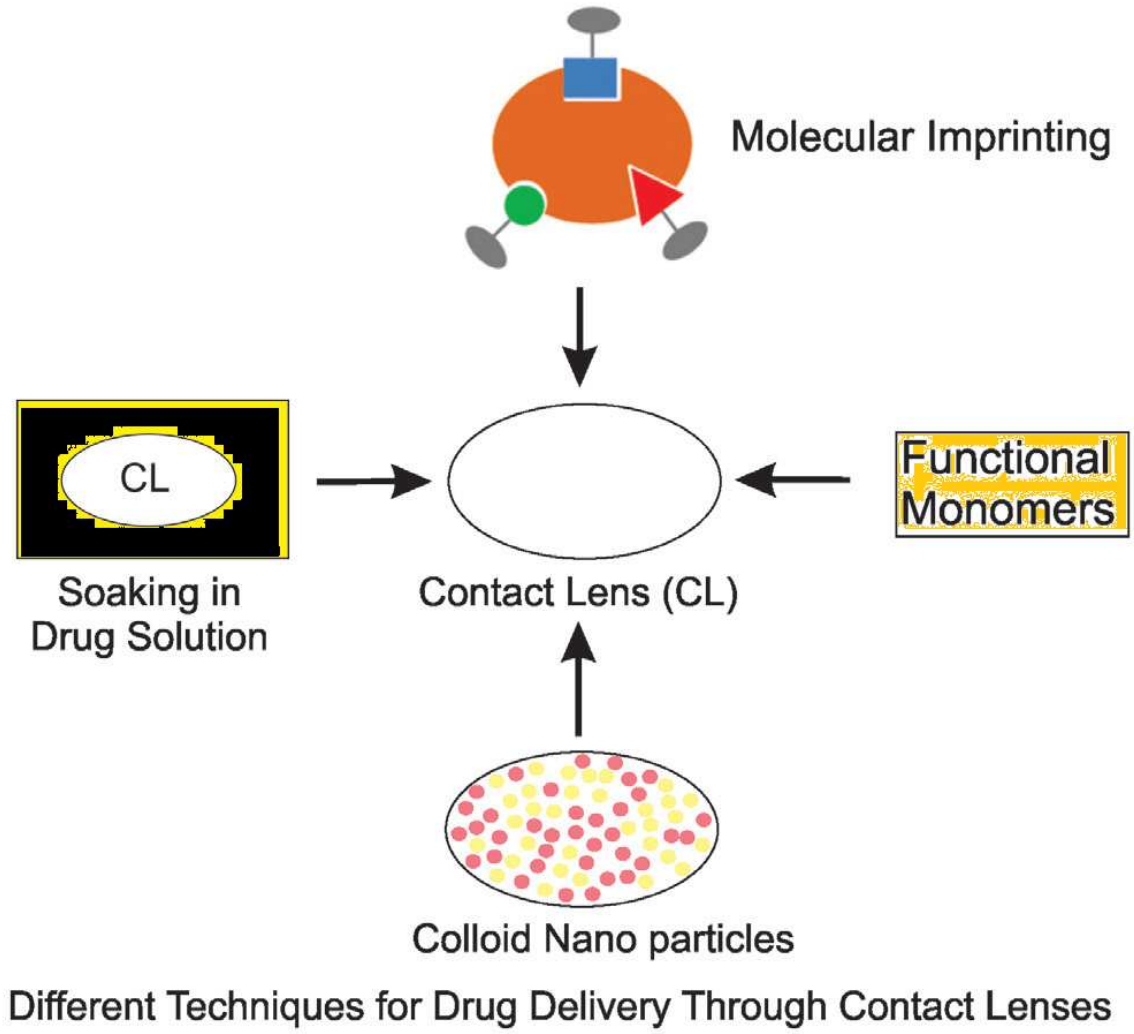

Fig 2 : Different Techniques for Drug Delivery through Contact Lenses

CONCLUSION

The use of contact lenses marked a tremendous development for the delivery of ocular drugs in a sustained or controlled or for prolonged period of time to the eye in an efficient manner. Contact lenses are used to treat many eye disorders which give moderate results. In contrast to all other parameters contact lenses can also be used for targeted drug delivery system. Based on the above mentioned criteria principally, contact lenses turned out to be satisfied drug delivery material for ocular drug delivery system.

REFERENCES

[1] McMahon TT, Zadnik K *Cornea* **2000**;19:730-740
[2] Sedlacek j. *Cesk Oftalmol* **1965**; 21:509-512
[3] Peppas NA,Huang Y ,Torres –Lugo M,Ward JH , Zhang j. *Annu Rev Biomed Eng* **2000**; 2:9 -29
[4] Kaufman HE ,Gasset AR. *Int Ophthalmol Clin* **1970** ;10:379-385
[5] Phan CM ,Hui A , Subbaraman L,Jones L. *Clin Exp Pharmacol* **2014**; 3:145
[6] Mawad D , Boughton EA ,Boughton P ,Lauto A. *Current Pharmaceutical Design* **2012**;18:2558-2575
[7] Covey M , Sweeney DF,Terry R ,Sankaridurg PR ,Holden BA. *Optom Vis Sci* **2001**; 78:95-99.
[8] Rathore K.S , Nema R.K. *Int J of Pharmaceutical Sciences and Drug Research* **2009** ; 1(1)
[9] Urtti A. *Adv Drug Deliv Rev* , 58 ,**2006** ,1131-1135
[10] Jtirvinena K,Tomi J ,Urttia SA..*Adv Drug Deliv Rev* ,16 ,**1995**,3-19
[11] Nanjawade BK ,Manvi FV ,Manjappa AS . *J Control Release* , 122 , **2007** , 119-134
[12] Reshu Sharma , Goswami Laxmi . *Int Research Journal Of Pharmacy* ,**2013**,4 (7)
[13] Le Bourlais C , Acar L,Zia H,Sado PA ,Needham T ,Leverge R. *Prog Retin Eye Res* **1998**;17:33-58
[14] Creech JL ,Chauhan A, Radke C. J. *I and EC* Res **1999**;40:3015-26

[15] Mc Namara NA ,Polse KA ,Brand RD ,Graham AD ,Chan JS ,Mc Kenney CD. *Am J Ophthal* **1999** ; 127: 659-665
[16] Saettone M. *Pharmatechnology* **2002**; 3:1 - 6
[17] Jung HJ , Jaoude MA ,Carbia BE ,Plummer C ,Chauhan A. *Journal of Controlled Release* **2013** ; 165:82-89
[18] Li CC , Chauhan A. *Ind Eng Chem Res* **2006**; 45:3718 -34
[19] Hui A , Sheardown H , Jones L. *Materials* **2012** ; 5:85 – 107
[20] Hehl EM , Beck R ,Luthard K,Guthoff R,Drewlow B. *Eur J Clin Pharmacol* **1999**; 55:317-23
[21] Ramaiyan Dhanapal , J.Vijaya Ratna .*Int Journal of Innovative Drug Discovery Vol – 2 / Issue* 1/**2012** /4-15
[22] Rathore K.S ,Nema R.K . *Int Journal of Pharmaceutical Sciences and Drug Research* **2009** ; 1(1)
[23] Sabzevar FT , Mohajeri SA. *Drug Dev Ind Pharm* **2014** ; 12:1-11
[24] Garcia DM ,Escobar JL ,Noa Y ,Bada N,Hernaez E ,Katime I.Timolol maleate release from pH – sensible poly(2-hydroxyethyl methacrylate – co-methacrylic acid *) Journal of hydrogels Eur Polym* **2004**;40:1683-90
[25] Ramaiyan Dhanapal , J.Vijaya Ratna. *Int Journal of Innovative Drug Discovery* Vol 2/*Issue* 1 /**2012** /4-15
[26] Mohammadi S ,Jones L ,Gorbet M. *PLoS One* **2014** *;* 9:e106653
[27] Kakisu K ,Matsunaga T , Kobayakawa S ,Sato T,Tochikubo T. *IOVS* **2013**;54:2551-61
[28] Gupta P , Vermani K ,Garg S. *DDT* **2002**;7:569-79
[29] Jain MR. *Journal of Ophthalmol* **1988**;72:150-4
[30] Jung Hj,Chauhan A. *Biomaterials* **2012**; 33:2289-300
[31] Xinming L , Yingde C ,Lloyd AW,Mikhalovsky SV , Sandeman SR, Howel CA. *Contact Lens and Anterior Eye* **2008**;31:57-64
[32] Hui A ,Willcox M ,Jones L. *OVS* **2014**;55:4896-904
[33] Karlgard CC , Wrong NS, Jones LW, Moresoli C. *Int Journal Pharm* **2003**;257:141-51
[34] 34.Bengani LC, Hsu KH, Gause S, Chauhan A. *Expert Opin Drug Deliv* **2013**;10:1483-96
[35] Atul Srivastava, D.V. Gowda, S.V. Madhunapantula, Chetan G.Shinde, M.Iyer. *Acta Pathol Microbiol Immunol Scand*.123, 275-288 (**2015**)
[36] Atul Srivastava, D.V Gowda , S.V. Madhunapantula , Siddaramaiah. Development and Efficacy Assessment of an Enteric Coated Porous Tablet Loaded With F4 Fimbriae for Oral Vaccination of Piglets against F4+ Enterotoxigenic Escherichia coli Infections. *Curr Drug Delivery*
[37] Atul Srivastava, D.V Gowda, Umme Hani, Chetan G. Shinde. *Journal of Biomater Tiss eng*. 4 ,804-810 (**2014**)
[38] D.V Gowda, Atul Srivastava, Rudra Vaghela. *Adv. Sci Eng. Med* 7 ,697-703 (**2015**)
[39] Atul Srivastava, D.V Gowda, Umme Hani, Chetan G.Shinde. *J.Biomater Tiss eng* .4 (718- 724 (**2014**).
[40] Atul Srivastava, D.V Gowda, T.M Pramod Kumar, Chetan G. Shinde. *J.Biomater Tiss eng*.4 (**2015**)