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Review Article

FORMULATION APPROACHES IN OCULAR DRUG DELIVERY SYSTEM

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Abstract:

The bioavailability of conventional ophthalmic solutions is very poor due to efficient protective mechanisms of the eye, blinking, reflex lachrymation and drainage which remove rapidly various foreign substances including drug from the surface of the eye. Frequent instillation of drug solution is necessary to maintain a therapeutic drug level in the tear or at the site of action but the frequent use of highly concentrated solution may induce toxic side effects due to systemic absorption of drug through nasolachrymal drainage. In recent years there has been significant efforts directed towards the development of new systems for ophthalmic drug delivery. This review focuses on recent literature regarding mucoadhesive systems, vesicular systems, semisolid hydrogel and in situ gelling system. Moreover, attempt has been made to explore the applicability of numerous polymers for ocular drug delivery system and also includes a detailed account on various recent strategies that are developed and under development stage so far.

Key words: Colloidal system; Hydrogel; In situ gel ;Iontophoresis; Mucoadhesive system;; Ocular inserts;.

1. Introduction

Many regions of the eye are relatively inaccessible to systematically administered drugs and as a result, topical drug delivery remains the preferred route in most cases. Drug may be delivered to treat the precorneal region for such infections as conjunctivitis and blepharitis, or to provide intraocular treatment via the cornea for diseases such as glaucoma and uveitis [1]. Various

approaches that have been attempted to increase the bioavailability and the duration of therapeutic action of ocular drugs can be divided into two categories. The first is based on the use of the drug delivery systems, which provide the controlled and continuous delivery of ophthalmic drugs. The second involves, maximizing corneal drug absorption and minimizing precorneal drug loss.

The bioavailability of ophthalmic drug is however, very poor due to efficient protective mechanisms of the eye, blinking, baseline and reflex lachrymation and drainage remove rapidly foreign substances, including drug, from the surface of the eye as shown in Fig.1. Moreover, the anatomy, physiology and the barrier function of the cornea compromise the rapid absorption of drug [2]. Frequent instillation of the eye drop is necessary to maintain a therapeutic drug level in the tear film or at the site of action but the frequent use of highly concentrated solution may induce toxic side effects [3].

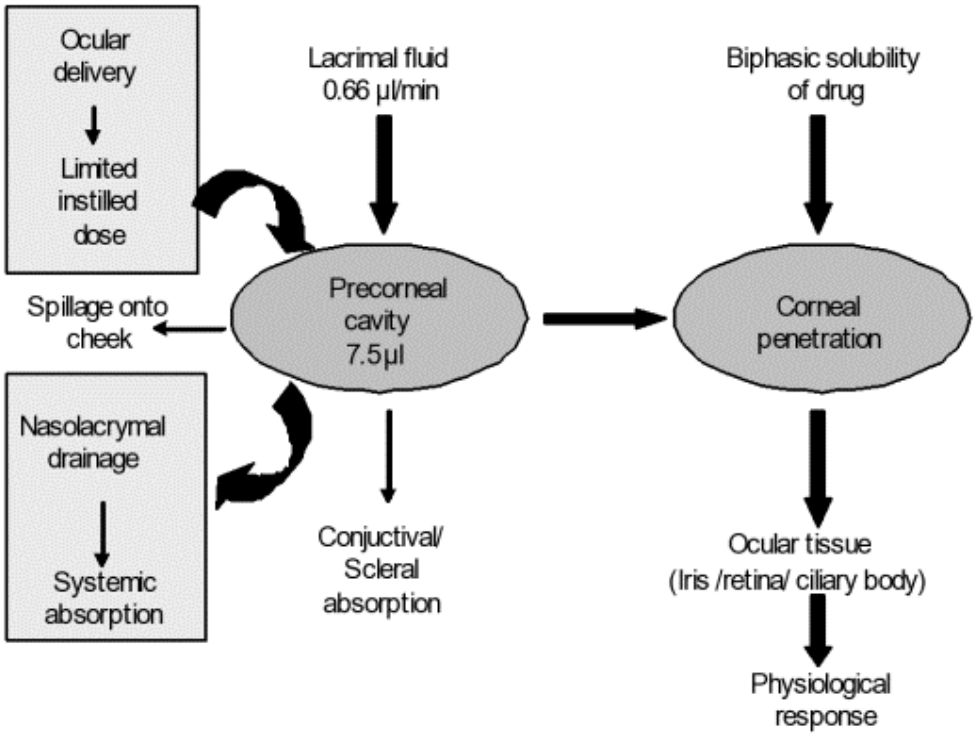


Fig.1 Factors attributing to poor bioavailability of ophthalmic formulation

Moreover, nasolachrymal drainage is also a major route to enter the circulatory system for drugs that applied through topical administration. For potent drugs, the systemic exposure through

nasolachrymal drainage after topical administration can be sufficiently high to cause systemic toxicity [4].

To enhance the amount of the active substances reaching the target tissue or exerting a local effect in the cul de sac, the residence time of drug in the tear should be lengthened. Moreover, once a day formulation should improve patient compliance. Recently, controlled and sustained drug delivery has become the standard in modern pharmaceutical design and an intensive research has been undertaken in achieving reliable, safety and feffective product. [5]. Numerous strategies were developed to increase the bioavailability of ophthalmic drugs by prolonging the contact time between the drug and cornea/ conjunctival epithelium. The use of a water soluble polymer to enhance the contact time and possibly also the penetration of the drug was first proposed by Swan [6].

Viscous semisolid preparations such as gels and ointments, proved a sustained contact with the eyes but they cause a sticky sensation, blurred vision and induce reflex blinking due to discomfort or even irritation [7]. Films, erodible and nonerodible inserts, rods and shields are the most versatile drug delivery systems aimed at remaining for a long period of time in the front of the eye. These systems sustained and control drug release and thus avoid pulsed entry.

Another approach has been the application of in situ gelling system or phase transition system [8,9,10]. A further approach to optimize the ocular dosage forms was the implementation of the mucoadhesive concept which was successful in buccal and oral application.

2. Ophthalmic disorders

Conditions treated by the topical application of the drugs include:

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.

Conjunctivitis: Inflammation of the conjunctiva which may be caused by bacterial and viral infection, pollen and other allergens, smoke and pollutants.

Dry eye syndrome: An inadequate wetting of the ocular surface.

Keratitis: Inflammation to cornea, caused by bacteria, viral, or fungal infection.

Iritis (anterior uveitis): Commonly has an acute onset with the patient suffering pain and inflammation of the eye.

Other conditions include the ophthalmic complications of Rosacea, blepharitis (inflammation of the lid margins), chalazia (Meibomian cysts of the eyelid), and corneal ulcer.

3. Ophthalmic drug delivery

The most common method of ocular drug delivery is the instillation of drops into the lower cul-de-sac. Eye drops provide pulsed entry of the drug followed by rapid decline in drug concentration, approximate to first order kinetics [11]. This form also have disadvantages; the very short time the solution stays at the eye surface, its poor bioavailability (a major portion i.e. 75% is lost via nasolacrimal drainage), the instability of the dissolved drug, and the necessity of using preservatives. The physiological factors attributing to poor bioavailability of eye drops shown in figure 1.

Due to low viscosity such drops are usually drained quickly, aided by blinking reflex, and the precorneal region returns to the normal resident of around 7µl.The retention of a solution in the eye is influenced by viscosity, hydrogen ion concentration, the osmolality and the instilled volume. To enhance the bioavailability and corneal contact time the polymers are added to ophthalmic solution and suspensions to increase the viscosity of the vehicle. It has been reported that an increase in the corneal penetration of a drug is at a maximum if the viscosity of the eye drop solution is about 15 to 150 mPa s (cp). Any increase in viscosity would have less effect on the drainage rate and tear film thickness and has been implicated with interference of vision and resisting movement of the eye lid Extensive work has been done to prolong ocular retention of drugs in the solution state by enhancing the viscosity or altering the pH of the solution [4-6].

3.1 Mucoadhesive polymers

The threshold required for successful mucoadhesion is a molecular weight of at least 100,000 Da. Excessive crosslinking in the polymer, however, decreases the chain length available

for interfacial penetration. Also excessive formation of interchain physical entanglement and hydrogen bonding within the polymer itself can lead to confirmation hindering polymer diffusion into the mucus layer [12,13]. Many high molecular weight polymers with different functional groups (such as carboxyl, hydroxyl, amino and sulphate) capable of forming hydrogen bonds and not crossing the biological membranes have been screened as a possible excipient in ocular delivery system [14]. Various viscosifying polymers screened for ocular mucoadhesive capacity are given in Table 1.

Table: 1

Viscosifying polymers screened for ocular mucoadhesive capacity.

Polymers	Charge	Mucoadhesive capacity
Poly (acrylic acid) neutralized	A	+++
Carbomer (neutralized)	A	+++
Hyaluronan	A	+++
Chitosan	C	++
Sodium carboxymethyl cellulose	A	++ (+)
Sodium alginate	A	++
Pectin	A	++ (+)
Xantan gum	A	+
Xyloglucan	A	+
Scleraglucan	A	+
Poloxamer	NI	+ (+)

Charge- A: anionic, C: cationic, NI: nonionic

Mucoadhesive capacity- + + +: excellent, + +: good, +: poor / absent

4.Hydrogel, In situ gelling system

Aqueous gel (hydrogel) consists of high molecular weight, hydrophilic, cross- linked polymers or co-polymers that form a three- dimensional network in water. These gels have been shown to combine significantly longer residence times in the cul-de-sac with increased drug bioavailability [11]. Kim et al define the hydrogels as polymers which have the ability to swell in water or aqueous solvents, and induce a liquid-gel transition [15]. The efficacy of ophthalmic hydrogel is mostly based on an increase of ocular residence time via enhanced viscosity and mucoadhesion properties. In particular, in situ gelling systems improve bioavailability and decrease the side effects induced by the systemic absorption of topically applied ophthalmic drugs [16]. Typical gelling agents include cellulose derivatives, polyvinyl alcohol, hyaluronic acid and carbomer. In situ gels are promising ocular drug delivery systems since they are conveniently dropped into the eye as a liquid where after they undergo a transition into a gel as a result of special physical / chemical changes (for example pH, temperature, and a specific ion) in their environment; in this case a cul-de-sac [17]. Due to their elastic properties hydrogels resist ocular drainage leading to longer contact times. Hydrogel is the mot common method of improving the ocular availability of drugs to increase precorneal residence time.

Qi et al. developed a thermosensitive in situ gelling and mucoadhesive ophthalmic drug delivery system containing puerarin based on poloxamer analogs and carbopol. The incorporation of carbopol 1342P NF not only did not affect the pseudoplastic behavior with hysteresis of the poloxamer analogs solution and leads to a higher shear stress at each shear rate, but also enhanced the mucoadhesive force significantly and sustained the drug release over a period of 8 h [17]. Kamel et al. developed a pluronic F 127 based formulations of timolol maleate (TM) aimed at enhancing its ocular bioavailability. In vivo study showed that the ocular bioavailability of TM, measured in albino rabbits, increased by 2.5 and 2.4 fold for PF127 gel formulation compared with 0.5% TM aqueous solution [18]. The mixture of 0.3% carbopol and 14% pluronic solutions

showed a significant enhancement in gel strength in the physiological condition. The pilocarpine release was extended upto 6h by using this system [19].

Miyazaki et al. were developed a thermoreversible gel formed in situ by aqueous solution of an enzyme degraded xyloglucan polysaccharide for sustained release vehicle for the ocular delivery of pilocarpine hydrochloride. [20].

Grafting of poloxamer onto the hyaluronic acid for in situ gelling ophthalmic drug delivery system for ciprofloxacin was reported by Cho et al [21]. Yanxia et al. investigated a novel thermosensitive copolymer (poly 9 N- isopropylacrylamide) –chitosan (PNIPAAm- Cs) for its thermosensitive in situ gel forming properties and potential utilization for ocular drug delivery for timolol maleate over a period of 12 h [22].

Edsman et al evaluated the rheological properties of deacetylated gellan gum (Gelrite®) and the effect of different ions in tear fluid (Na^+, K^+, Ca^{2+}) on the gel strength [23]. Pandit et al developed the in situ gelling system for Indomethacin by using ion sensitive sodium alginate. The release of indomethacin was extended upto 8 h, and [24].

Mourice and Srinivas found a two fold increase in the permeation of fluoroscein in humans by using gellan gum compared to an isotonic buffer solution [25]. Pan et al. developed ophthalmic system of gatifloxacin using alginate (Kelton®) in combination with HPMC (methocel E50LV) which acted as a viscosity enhancing agents. In vivo precorneal retention studies indicated that the alginate / HPMC solution retained the drug better than the alginate or HPMC alone [26].

The pH triggered in situ gel of antibacterial agent; ofloxacin for ophthalmic delivery was developed by Srividya et al. Polyacrylic acid (Carbopol® 940) [27]. Polycarbophil based pH triggered in situ gelling system was reported. Polycarbophil is insoluble in water, but its high swelling capacity in a neutral medium permits the entanglement of the polymer chains with the mucus layer [28].

Lindell and Engstrom reported an in situ thermogelling system consisting of ethyl (hydroxyethyl) cellulose and a charged surfactant releasing slowly timolol maleate [29].

Pluronic F-127-g-poly (acrylic acid) copolymer based in situ gelling vehicle was found to have prolonged precoeneal residence time and improved ocular bioavailability. The studies indicated that the drug release rates decreased as acrylic acid / pluronic molar ratio and copolymer solution concentration increased [30]. Sol-to-gel system of ciprofloxacin hydrochloride was prepared by utilizing the phase transition properties of hydroxyl propylmethyl cellulose K15M and carbopol 934 [31]. Lui et al developed Aginate / HPMC based system for long acting delivery of gatifloxacin [32].

5. Colloidal system

5.1 Microspheres and Nanparticle

The rational for the development of various particulate systems for the delivery of ophthalmic drugs was based on possible entrapment of the articles in the ocular mucous layer and the interaction of bioadhesive polymer chain with mucins including a prolonged residence and slow drainage. Furthermore controlled drug release and enhanced absorption or even endocytosis in the case of nanoparticles should improve bioavailability [33].

The first particular colloidal carrier system developed was Piloplex ®, consisting of pilocarpine sonically bound to poly (methyl) methacrylate-co-acrylic acid nanoparticles [33]. According to Klein et al., twice daily instillation of pilocarpine in glaucoma patients are as effective as 3 to 6 instillation of conventional pilocarpine eye drop per day [34]. Santos et al. designed the microsphere for sustained delivery and enhanced intracellular penetration for ocular administration of antisense oligonucleotides. Nanosized complexes of antisense TGF-²2 phosphorothioate oligonucleotides (PS-ODN) with polyethylnimine (PEI) and naked POS-ODN were encapsulated into poly (lactide-co- glycolide) microsphere prepared by the double emulsion evaporation method [35]. Gaini et al. formulated poly (lactide-co-glycolide) microsphere as a carrier for the topical ocular delivery of peptide drug vancomycin with high and prolonged vancomycin concentration and increased AUC values (Two fold) with respect to an aqueous solution of the drug. [36].

The formulation developed of rhVEFG in poly (D, L-lactide–co-glycolide) (PLG) microsphere that provide a continuous local delivery of intact protein. [37]. Sorin et al. developed a new ophthalmic delivery system, pilocarpine loaded proteinaceous (gelatin albumin) microspheres for better ocular bioavailability [38].

Various mucoadhesive polymers have been tried to prepare the microspheres and nanoparticles to increase the total bioavailability and effectiveness of the dosage form like Acrylate [39]. The hydrophilic Polyalkyl- (Cyanoacrylates) (PACA) and polyalkyl methacrylate were most commonly used for the preparation of drug carriers in the size range 200-500nm, for sustained drug release and prolonged therapeutic effect [40]. Zimmer et al. showed that poly (butylcyanoacrylate) nanoparticles were taken up in the first cell layers of the cornea and conjunctiva by endocytosis or due to lysis of the cell membrane resulting from the degradation of the product. [41]. Pignatello et al. employed copolymers of poly (ethylacrylate), poly (methylmethacrylate) and poly (chloromethyl-aminomethyl methacrylate containing quaternary groups (4.5-6.8% and 8.8 -12%) for Eudragit® RS and RL respectively [42-44].

Gupta et al. developed polymeric micelles made of a copolymer of N-isopropylacrylamide, vinyl pyrrolidone and acrylic acid cross-linked with N, N'- methylene bis-acrylamide, in which the water insoluble drug ketorolac (free acid) was entrapped [45].

Hsiue et al. investigated the use of the thermosensitive polymer poly-n – isopropylacrylamide (PNIPAAm) in controlled release delivery system for glaucoma therapy [46]. Micro and nanoparticles made of poly (D, L.-lactide-co-glycolide) (PLGA) were investigated for topical application. [47].

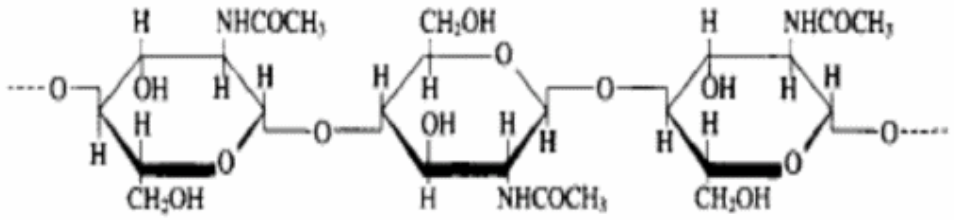
Ginnavola et al changed the surface properties of the PLA nanoparticles loaded with acyclovir by the incorporation of pegylated 1,2 distearyl-3 phosphotidyl ethanolamine (DSPE-PEA) [48] instead of coating the external surface as in case of PACA nanoparticles [49]. Gelatin nanoparticles encapsulating pilocarpine HCl or hydrocortisone as model drug were prepared using desolvation method by J.Vandervoot and A. Ludwig. [50].

Hyaluronan and its chemical derivatives were also employed to prepare micro and nanoparticles. The release of methyl prednisolone from particles consisting of hyaluronic acid esters has been evaluated in vitro and in vivo on rabbits by kyyronen et al. [51].

Chitosan is an interesting polymer to formulate micro and nanoparticles due to mucoadhesive and permeability enhancing properties and its biodegradability by lysozyme [52]. Genta et al. have been compared the acyclovir loaded chitosan microsphere with aqueous suspension, an increase of about 4 fold in aqueous humour concentration of acyclovir after a single instillation of acyclovir loaded chitosan microsphere [53]. Chitosan microspheres and nanoparticles have a higher precorneal retention than chitosan solution, and depending on the size the nanoparticles may enter the corneal epithelium to a certain depth by a paracellular or transcellular pathway [54]. Nanosystem having surface aggregated chitosan or polyethylene glycol was found relatively stable and also efficient at overcoming mucosal barrier. Chitosan interacts with mucin as shown in figure 2.

Figure: 2

(a)



b)

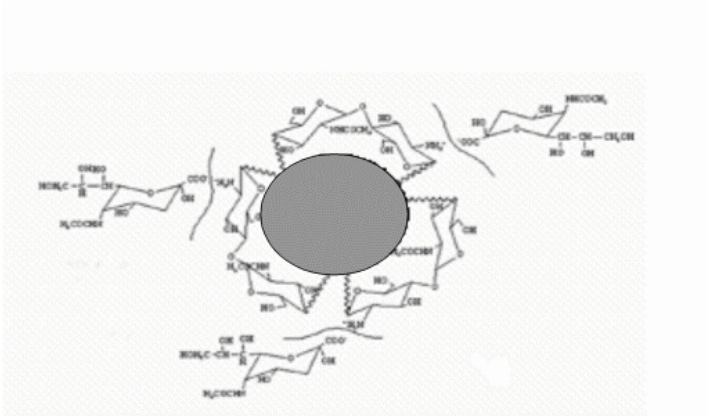


Fig 2 a) structure of chitosan, a biopolymer obtained hydrolytically from chitin of crustacean shell

b) Interaction between chitosan coated nanoparicles and sialic acid presesnt in the mucin layer is expected to improve bioavailability.

Polysaccharide like pectin used for the preperation of piroxicam nanoparticles with 205 fold increased drug absorption compare to eye drop solution[55].

Various in vivo studies in rabbits reported the prolonged effect of drugs (Pilocarpine, Piroxicam) incorporated in albumin particles compared to commercial preparations or aqueous and viscous [56,57]. Zimmer et al. and Marta Mmerodio et al. Developed the albumin loaded colloidal system for pilocarpine and gancyclovir respectively. [58,59].

Solid lipid nanoparticles observed with longer retention time on the corneal surface and in the cul-de-sac is probably due to their small size. The nanoparticles are presumably entrapped and retained in the mucus layer. Cavalli et al. evaluated the use of solid lipid nanoparticles (SLV) as carrier for tobramycin [60]. Compared to commercial eye drops, the tobramycin –loaded SLN produced a significantly higher bioavailability with no any ocular irritation.

Imprinted polymers are increasingly considered for biomedical applications, including drug delivery. Feedback regulated drug delivery may be achievable by a combination of imprinted, stimuli sensitive materials that would allow high drug-loading capacity molecularly imprinted polymers (MIP's) to respond to external stimuli (slight changes in pH, temperature, ionic strength, concentration of biomolecules, or presence of specific receptors, and / or ligands) and modulate the affinity of the network for the target molecules (bioactives), thus providing a regulatory capability for the release process as in figure. 3.

Figure: 3

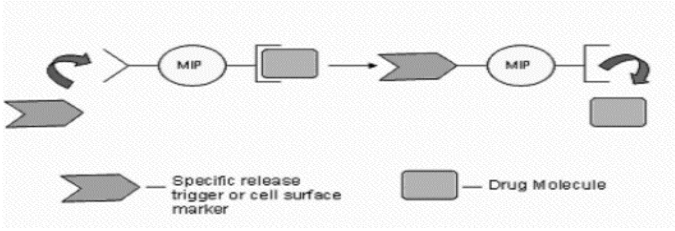


Fig-3: Schematic representation of targeted drug delivery and intelligent active release with a molecularly imprinted carrier

Colloidal nanosystem based on biodegradable polymeric materials that combine the capabilities of stimulus response and molecular recognition promises significant improvement in the ocular delivery of therapeutic agents. The formulation of biodegradable polymers as colloidal system holds significant promise for ophthalmic drug delivery. Additionaly, surface modified nanoparticulate carriers may use to accommodate a variety of actives [61] as in figure 4.

Figure 4:

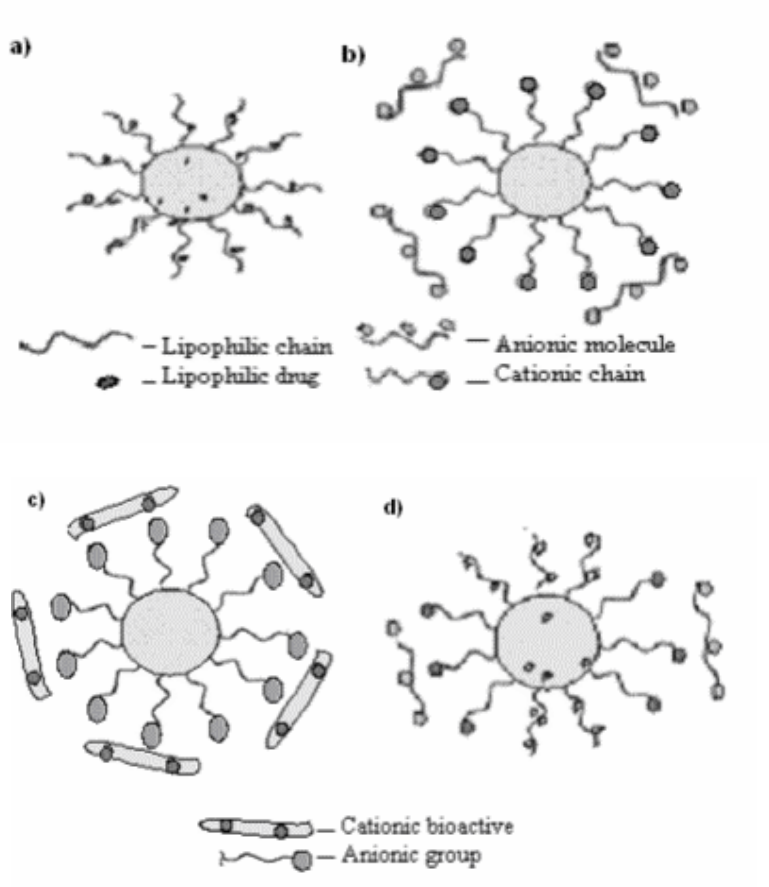


Fig 4- Nanoparticles

a) Lipophilic nanoparticles

(b, c) Ionic nanoparticles nanoparticles

(d) Amphiphilic nanoparticles

6.Vesicular system

Vesicular systems not only helps in providing prolonged and controlled action at the corneal surface but also helps in providing controlled ocular delivery by preventing the metabolism of the drug from the enzymes present at the tear/corneal epithelial surface. Moreover, vesicles offer a promising avenue to fulfill the need for an ophthalmic drug delivery system that has the convenience of a drop, but will localize and maintain drug activity at its site of action. The rate of drug penetration depends not only on the physicochemical properties of the drug itself. [62]. Vesicular drug delivery systems used in ophthalmics broadly include liposomes and niosomes [63]. Liposomes are the microscopic vesicles composed of one or more concentric lipid bilayers, separated by water or aqueous buffer compartments with a diameter ranging from 80 nm to 10μ m. Liposomes (also called phospholipid vesicles) were first described by Bengham A. D. [64]. Such vesicles (Fig. 5) composed of one or more phospholipid bilayer membranes can entrap both hydrophilic and hydrophobic drugs, depending on the nature of the drug and hence, it is possible to apply water-insoluble drugs in liquid dosage form. According to their size, liposomes are known as either small unilamellar vesicles (SUV) (10–100 nm) or large unilamellar vesicles (LUV) (100–3000 nm). If more than one bilayers are present, then they are referred to as multilamellar vesicles (MLV).

Figure: 5

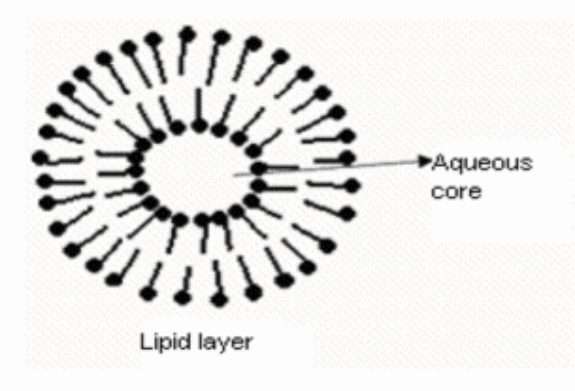


Fig-5 Basic structure of vesicular system

Liposomes can act as carriers for a wide variety of drug molecules, proteins, nucleotides, and even plasmid endowing them with a great potential for their application in ophthalmics [65]. Another potential advantage of liposomes is their ability to come in an intimate contact with the corneal and conjunctival surfaces, thereby, increasing the probability of ocular drug absorption [66]. This ability is especially desirable for drugs that are poorly absorbed, for example, the drugs with low partition coefficient, poor solubility or those with medium to high molecular weight [66] and enzymes, like cholinesterase [67].

Positively charged liposomes on the other hand were reported to exhibit a prolonged precorneal retention, than neutral and negatively charged liposomes because of electrostatic interaction with the negatively charged corneal epithelium. It is proposed that these liposomes bind intimately on the eye surface, increase the residence time and thus drug absorption [68].

Liposomes were used by Dean et al. [69] for nuclear targeting of plasmid DNA in human corneal cells. Similarly, liposomes were used for intravitreal administration of oligonucleotides for the treatment of ocular viral infections, like Herpes simplex virus or Cytomegalovirus (CMV) [70].

In order to enhance adherence to the corneal, conjuctival surface, dispersion of the liposomes in mucoadhesive gels or coating the liposomes with mucoadhesive gel or wetting the liposomes with mucoadhesive polymers was proposed [71]. Several mucoadhesive polymers were employed which includes poly (acrylic acid) (PAA), hyaluronic acid (HA), chitosan and poloxamers [72, 73,74, 75]

The positively charged liposomes are more effective than negatively charged and neutral liposomes [68].

Dendrimers

Synthetic, spherical, macromolecules named after their characteristic tree like or dendritic branching around a central core, which possess unique properties (multivalency, globular architecture and well defined molecular weight) that makes them a new scaffolds for drug delivery, especially if formulated as micelles may prove effective vehicles for ocular drug delivery [61].

Vandamme developed poly (amidoamine) (PAMAM) dendrimers for controlled ocular drug delivery of pilocarpine and tropicamide [76]. Devarakonda designed Polyamidoamine (PAMAM) Dendrimers for Water-Insoluble Nifedipine [77]. Marano et al have have performed a long-term study into the use of a lipophilic amino-acid dendrimer to deliver an anti-vascular endothelial growth factor (VEGF) oligonucleotide (ODN-1) into the eyes of rats and inhibit laser-induced choroidal neovascularization (CNV) [78]. The polymer micelle is a particle fundamentally formed with a hydrophilic polymer chain as a shell and a hydrophobic polymer chain as core. The drug delivery system of the invention can be effectively applied to photodyanamic therapies, when a photosensitive drug used as a drug and can be subjected to therapy for age related macular degeneration through occluding choroidal new vessels [79].

7. Solid dosage forms

Ocular inserts

Films, erodible and nonerodible inserts, rods shields are the most logical delivery systems aimed at remaining for a long period of time in the front of the eye, listed in table 2 [86-94].

Table2 various ocular inserts:

Name	Description
SODI (soluble ocular drug insert) [86] of a soluble acrylamide, N-	Small oval wafer, composed Co-polymer consisting of vinyl pyrrolidone and ethyl softens on insertion
NODS(New or novel ophthalmic delivery system)[87]	Medicated solid polyvilnyl alcohol flag that is attached to a paper covered handle, an application flag detaches and gradually dissolves, releasing the drug.
Collagen shields [88]	Erodible discs composed of crosslinked porcine scleral collagen.
Ocusert [89]	Flat, flexible elliptical insoluble device consisting of two layers enclosing a reservoir, used commercially to deliver pilocarpine for 7 days.
(OTS) Minidiscs or ocular therapeutic system [90]	4-5 mm diameter contoured either hydrophilic or hydrophobic disc.
Lacrisert [90]	Rod shaped device made from hydroxy propyl used in the treatment of dry eye syndrome as an alternative to artificial tears.
Ophthalmic inserts [91]	A cylindrical device containing mixtures of silicone elastomer and sodium chloride as a release modifier with a stable polyacrylic acid (PAA) interpenetrating polymer network grafted on to surface
Bioadhesive ophthalmic drug insert (BODI) [92]	Adhesive rods based on mixtures of hydroxypropyl hydroxypropyl cellulose ethyl cellulose, polyacrylic acid, cellulose acetate phthalate.
Dry drop [93]	A preservative free drop of hydrophilic polymer solution (hydroxyl propyl methyl cellulose) that is freeze dried on the tip of a soft hydrophobic carrier strip, immediately hydrates in the tear film.
Gelfoam [94]	Slabs of Gelfoam Impregnating with mixtures of drug and cetyl ester wax in chloroform.

However, the inserts were not well tolerated or accepted by patients due to difficulties encountered in the application, psychological factors and possible interference with vision [81]. Various researchers have developed and performed In vivo studies solid inserts by using various polymer combinations [82, 83, 84, 85]

New devices for sustained release are being developed that allow the maintenance of a more constant level of these compound in the posterior segment, for example- sustained release flucinolone acetonide intravitrial implants (Retisert), significantly reduced uveitis recurrences, improved visual acuity and decreased the need for adjunctive therapy in the patient population studies [95]. Similarly biodegradable polymeric scleral plug that delivered sustained release of tacrolimus (FK 506) in a rabbit model of experimental uveitis [96]. A biodegradable, deep scleral lamear cyclosporine, a device, which was placed near to or in contact levels of drug to the uveal tissues in the equine eyes [97].

8. Iontophoresis

Iontophoresis ia advanced non-invasive technique for ocular drug delivery. [98] Transcorneal iontophoresis is iused to drive charged drug by an electric current into the cornea. In a pseudomonas model model of bacterial keratitis, as well as in pharmacokinetic studies, ocular iontophoresis of gentamycin, tobramycin, or ciprofloxacin was superior to topical ocular drops for reducing pseudomonas in the cornea. This method was shown to be safe and nontoxic to the rabbit corneal epithelium [99].

Molokhia et al. studied the transcorneal iontophoretic delivery and compared to passive delivery and intravitrial injection using nuclear magnetic resonance imaging (MRI) and employed the MRI to investgate the factors affecting transcorneal iontophoretic delivery [100]. Extending the duration of iontophoresis at this site allowed the drug to be delivered into the vitreous more deeply and to the greater extent than when the application site was at the back of the eye near the fornix. The results showed that electrode placement was an important factor in transscleral iontophoresis

and the ciliary body (pars plana) was determined to be the pathway of least resistance for iontophoresis transport.

The major causes of blindness in the United State and Europe are age related macular degeneration (AMD) and diabetic retinopathy (DR). Posterior uvietis and retinitis secondary to glaucoma also contribute considerably to loss of vision. These conditions affect tissues at the back of the eye, where drug treatment is difficult to administer. Current method for ocular delivery have limitations, invasive methods are inherently risky due to the potential for bleeding, infection, retinal detachment and other local injuries. To meet these needs Iomed, Inc. is developing a novel ocular iontophoresis system (OcuPhor^{TM}) to deliver drugs safely and noninvasively to the back of the eye [101].

The OcuPhor^{TM} system consists of drug application dispersive electrode and an electronic iontophoresis dose controller. A hydrogel pad to absorb the drug formulation and a small flexible wire to connect the conductive element to the dose controller. The drug pad is hydrated with drug solution immediately prior to use and the applicator is placed on the sclera of the eye under the lower eye lid. Preliminary clinical studies in human volunteers have shown that the OcuPhor ^{TM} system is well tolerated over a wide range of both positive and negative polarity current and does not produce any ophthalmic changes as measured by a series of standard tests.[102]

Iomed used a model anionic drug, diclofenac to investigate the interstudy and intrastudy reproducibility of transscleral iontophoresis to rabbit eyes. Significant amount of diclofenac was found in retina / choroid tissues on average iontophoresis resulted in approximately a 16-fold increase of diclofenac concentration in retina choroid as compared to passive no current control. Relatively small amount of drug were delivered systemically, indicating predominantly local delivery to the eye, with the transscleral Iontophoresis [101].

9. Recent developments in ocular drug delivery system

Challenges for effective front of the eye (FOTE) drug delivery include somehow minimizing the use of preservatives in the drug solution being applied, and avoiding excess eye

drop solution being drained through the nasolachrymal duct with potential systemic absorption into the circulatory system.

Currently available devices for improving FOTE drug delivery using eye drops include the Visine pure tears single drop dispenser, which contains no preservatives. The Pfizer Xal-ease FOTE drop delivery device which encloses a traditional eye drop bottle and the Autosqueeze and Autodrop devices developed in the UK, with Royal national Institute for the Blind, which clip into bottles of the eye drop.

Recent innovations in FOTE drug delivery devices include the Eye-Instill produced by Med-Instill Inc., which have one way valve to ensure multiple dosings of sterile, preservative free drug solution and the OptiMyst device, which dispenses medication as a mist rather than as a drop. The latter provides much less medication per dose, below blink and lachrymation thresholds.

The VersiDoser ^{TM} drug delivery system under development by Mystic pharmacueticals, Inc., holds the near term potential for setting new slandard for effective FOTE drug delivery. The VersiDoser platform utilizes the pack with Novel multidose delivery device that dispenses the drug into the eye in a predictable manner irrespective of the orientation of the device and the eye. These devices are capable of the self administered precision dosing in the 12-15µl range and provide automatic dose counters. Preservative free packaging and ergonomic design will significantly enhance compliance, ease of use and therapeutic benefits for elderly and padiatric patients [103].

10. Conclusion

Formulating a drug delivery system for the sensitive organ like eye always remains a challenge for the formulation chemist. Though intensive work has been done on this drug delivery system still there is no such formulation which increases patient compliance and reduces side effects due to systemic absorption of drug substances. Number of new approaches is being used but still need to work on this important drug delivery system.

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