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COMPENSATORY STRATEGY ON OCULAR DRUG DELIVERY SYSTEM

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ABSTRACT

Ocular anatomy and physiology is very unique which is why it creates a challenge in developing drugs given by ocular routes. The Eye has several layers of tissues in it. This route is extremely effective due to its rapid onset of action and small dose requirement. Transcorneal penetration is the route of absorption of drug. Several different dosage forms are being developed e.g nanoparticles, liposomes, nanomicelles and microemulsion to overcome difficulties in drug delivery by this route. This review focused on ocular drug delivery has become the standard in modern pharmaceutical design and several possible routes of drug delivery into the ocular tissues.

KEY WORDS: Ophthalmic drug delivery, Novel drug delivery, Occusert, Eye, gel.

INTRODUCTION

Drug disposition characteristics make eye an interesting organ. Usually drug applying by topical application is the best choice in cases of safety. The most challenging part is to develop a dosage form that will pass the layers of eyes without causing a damage to them. Development of new and more effective diagnostic techniques and novel therapeutic agents provide high therapeutic bioavailability of drug. The aim is to design a drug that remains in the ocular cavity for a desired duration. Ocular anatomy and physiology as well as physicochemical property of therapeutic agent is responsible for disposition and elimination. Ocular drugs can be divided into two categories based on their therapeutic action. The first one is to provide a continuous and controlled delivery of drugs using a sustained drug delivery systems. The second is minimizing precorneal drug loss and maximizing corneal drug absorption. When drug is applied by conventional droppers which delivers 50-75µl per drops, much of the drop portion rapidly drains until the eye is back to normal resident volume of 7µl. Therefore very small drug is available to enter the cornea and inner tissue of the eye. Actual corneal permeability of the drug is relatively low and very small corneal contact time (about 1-2 min) in humans for instilled solution usually less than 10% [1,2]. Therefore only small amount of drug actually penetrates the cornea and reaches intraocular tissue [3,4]. Due to these limitations, Controlled drug delivery to the eye is restricted imposed by the efficient protective mechanism. An ideal ophthalmic drug delivery must be able to release the drug in sustained manner and to remain in the area of front of the eye for prolong period of time. As a result it is necessary to optimize ophthalmic drug delivery; the best way to do so is by adding of polymers of various grades, development of colloidal suspension or using erodible or non erodible insert, development of viscous gel to prolong the precorneal drug retention [5 ,6]. Microparticle suspension [7] or polymeric solution [8] can be bioadhesive systems. For small and medium sized peptides major resistance is not size of the compounds (present in formulation) but charge, it is found that resistance to negatively charged compounds is more as compared to positively charged compounds to the cornea [9].

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As in situ activated gel forming systems can be administered in drop form and create considerably fewer problems with vision so that it is most preferable type of delivery system. Furthermore, In situ activated gel forming systems provide better sustained release properties than drops. This type of dosage forms are used now a day in various type of eye disease like combat glaucoma, dry eye syndrome, eye infection etc [10].

The Anatomy and Physiology of the Eye:

The eye is a very crucial sense organ of the body and its anatomy is quite complex. Refracted light produces a focused image on the eye that can stimulate nervous system and ensures the capability to see. Eye is able to refract light and produce a focused image that can stimulate nervous system and enable the ability to see.

The Structure of the eye and different Parts of the eye:

Choroid: The choroid layer is located behind the retina and absorbs unused radiation.

Aqueous Humour: It is a jelly-like substance located in the anterior chamber of the eye.

Ciliary Muscle: The ciliary muscle is a ring-shaped muscle attached to the iris. It is important because contraction and relaxation of the ciliary muscle controls the shape of the lens.

Cornea: Cornea is a clear transparent epithelial membrane. Light rays pass through the cornea to reach the retina. The cornea is convex anteriorly and is involved in refracting (bending) light rays to focus them on the retina.

Fovea: The fovea is a small depression (approx. 1.5 mm in diameter) in the retina. This is the part of the retina in which high-resolutionvision offine detail is possible.

Hyaloid: The hyaloid diaphragm divides the aqueous humour from the vitreous humour

Iris: The iris is the visible coloured part of the eye and extends anteriorly from the ciliary body, lying behind the cornea and in front of the lens. It divides the anterior segment of the eye into anterior and posterior chambers which contain aqueous fluid secreted by the ciliary body. The iris is supplied by parasympathetic and sympathetic nerves. Parasympathetic stimulation constricts the pupil and sympathetic stimulation dilates it.

Lens: The lens of the eye is a flexible unit that consists of layers of tissue enclosed in a tough capsule. It is suspended from the ciliary muscles by the zonule fibers.

Optic Nerve: The optic nerve is the second cranial nerve and is responsible for vision. Each nerve contains approximately one million fibres transmitting information from the rod and cone cells of the retina.

Papilla: The papilla is also known as the "blind spot" and is located at the position from which the optic nerve leaves the retina.

Pupil: The pupil is the aperture through which light - and hence the images we see and "perceive" - enters the eye. This is formed by the iris. As the size of the iris increases (or decreases) the size of the pupil decreases (or increases) correspondingly.

Retina: The retina may be described as the "screen" on which an image is formed by light that has passed into the eye via the cornea, aqueous humour, pupil, lens, then the hyaloid and finally the vitreous humour before reaching the retina. The retina contains photosensitive elements (called rods and cones) that convert the light they detect into nerve impulses that are then sent onto the brain along the optic nerve.

Sclera: The sclera is a tough white sheath around the outside of the eye-ball. It consists of a membrane that maintains the shape of the eye and gives the attachment to the extrinsic muscle of the eye.

Vitreous Humour: The vitreous humour (vitreous body) is a jelly-like substance.

Advantages of Ocular Drug Delivery Systems:

Various advantages of ocular drug delivery system are given below.

1.Easy convenience and needle free drug application without the need of trained personnel assistance for the application, self medication, thus improving patient compliances compared to parenteral routes. Good penetration of hydrophilic, low molecular weight drugs can be obtained through the eye.

2.Rapid absorption and faston set of action because of largeabsorptionsurfaceareaandhighvascularisation.Ocularad ministrationof suitable drug would therefore be effective in emergency therapy as an alternative to other administration routes.

3. Avoidance of hepatic first pass metabolism and thus potential for dose reduction compared to oral delivery.

Disadvantages: Various disadvantages of ocular drug delivery system are given below. [11,12].

1.The physiological restriction is the limited permeability of cornea resulting into low absorption of ophthalmic drugs.

2.A major portion of the administered dose drains into the lacrimal duct and thus can cause unwanted systemic side

effects.

3.The rapid elimination of the drug through the eye blinking and tear flow results in a short duration of the therapeutic effect resulting in a frequent dosing regimen

Ophthalmic Dosage Forms:

The most common method of ocular drug delivery is the instillation of drops into the lower cul-de-sac. The concentration of drug in the precorneal area provides the driving force for its transport across the cornea via passive diffusion. Once an inactive ingredient has been approved for a product through a particular route of administra-tion, it can be used in any new drug[13].Thus, efficient ocular drug absorption requires good corneal penetration as well as prolonged contact time with the corneal tissue.

Liquids:

Eye drops/lotion- Eye drops may be solutions or suspensions and are comparatively convenient, safe, immediately active and acceptable to patients. An eye drops is sterile, contains a preservative (if not singly used only), is isotonic, has a pH of about 7.4 for the patient comfort and has a limited shelf life after opening (if used more than one time). Eye lotions are isotonic, sterile solutions for the irrigation of the eye, usually as a single use first aid treatment [14].Polymers are frequently added to ophthalmic solutions and suspense ons in order to increase the viscosity of the vehicle, this prolongs contact with the cornea, so that enhancing bioavailability [15]. Generally, the high molecular weight hydrophilic polymers those are unlikely to cross the biological membrane. They include poly vinyl alcohol, hyaluronic acid, dextran, gellan, methylcellulose, hydroxymethylcellulose [16,17].

Eye Ointments:

Ointments are the semi solid preparations intended for external application. They are usually formulated using mixture of semisolid and solid hydrocarbons (paraffin) which have a melting or softening point close to the body temperature and are nonirritating to the eye. Ointments are useful in improving the drug bioavailability and in sustaining drug release. Ointments suffer with relatively poor patient compliance due to blurring of vision. So, they are often used as night time medication [18].

Aqueous Gel:

Aqueous gel (hydrogels) consists of high molecular weight, cross linked polymers that form a three dimensional network in water. Hydrogels are based on the addition of hydrocolloids to aqueous drug solutions. The most common polymers are used in such formulation are cellulose derivatives, carbomers, polysaccharides, polyvinyl alcohol, polyvinyl pyrrolidone and hyaluronic acid. Gels permit longer residence time in the precorneal area then viscous solution. The most important advantage of gel is increase in the contact time of the drug to the tissue. So, that drug can remain for longer period at the desired site [19].

Microspheres and Nanoparticales:

These are the promising drug carriers for ophthalmic applications; the drug absorption is enhanced significantly in the eye in comparison to eye drop solution owing to the much slower ocular elimination rate of particles. Smaller particles are better tolerated by the patients than longer particles therefore nanoparticles may represent very comfortable.ophthalmic prolonged action delivery systems. However, albumin microspheres reportedly cause adverse reaction in the eye [19]. Nanotech could end up providing a solution to the need for bulky headsets in virtual reality environments, and theanswer involves contact lenses[20].

Present investigation on Ophthalmic Drug Delivery System:

It developed ophthalmic suspension of prednisolone acetate (1%). This formulation is useful to obtain a better contactibility of the drug at the desired site of action[21]. During the formulation of prednisolone ophthalmic suspension its physicochemical, physiological and pharmaceutical parameters were evaluated. The type of process selection requires thorough knowledge of physicochemical properties of the drug, excipients, required flow and release properties, etc[22]. While viscosity enhancer, preservative, chelating agent were also included in the formulation to increase the transient residence time, antimicrobial preservation respectively and isotonicity of the formulation was also maintained by the addition of tonicity modifiers. Buffering agents used were having buffering capacity NMT 0.05% and pH was adjusted at which prednisolone acetate was stable. The finished product subjected to keep stress conditions to ensure the physical stability of the formulation. The formulation was packed in LDPE plastic vials and then carried out the accelerated stability studies at 40°C and the kinetic and the degradation rate constant and shelf life determined according to the predictive method. The results showed that the development of a new ophthalmic formulation having considerably better contact time by the selection and optimization of viscosity (HPMC) that obtained (21 cps) with better stability studies. Finally, the results concluded that prednisolone acetate 1.0 per cent ophthalmic suspension is much effective than prednisolone phosphate 1.0 per cent ophthalmic solution in suppressing corneal inflammation [21]. It prepared egg albumin microspheres of pilocarpine nitrate by using the heat stabilization method[23]. Factors that affect the size and encapsulation efficiency were optimized to obtain microspheres in the size range 1 to 12 ìm to make them undetectable by eyes and sufficient to entrap drug efficiently.

Encapsulation efficiency of egg albumin microspheres was found to be that was to be 63.4%. By

using spherical matrix *in vitro* release of drug was evaluated. In the preparation of microsphere gel Carbopol–940 polymer was used. Comparative evaluations were made by preparing simple gels of same drug concentration. Bioavailability parameters of all the formulations were evaluated and comparisons were made [23].

It reported that mucoadhesive microspherescan be prepared bydifferent methods and was evaluated for theirmucoadhesive properties [24] . The microsphere prepared by glutaraldehyde (as a crosslinking agent) and thermal cross linking showed good stability in HCl as compared with microsphere prepared by tripolyphosphate and emulsification ionotropic gelation method. In controlled and targeted drug delivery system, microspheres can be used because it overcomes the problems associated with conventional drug delivery like poor absorption, less contact time and poor bioavailability [25]. For certain drugs that have non-concentration dependent pharmacodynamics, such as etalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration[26]. It prepared and evaluated the liposomes of brimonidine tartrate and they were found that liposomes are the efficient vesicular carrier system for therapeutic effectiveness in terms of duration of action and decrease in dose frequency[25]. The *in vitro* and *ex- in vitro* drug release studies profile showed that, there was slow and prolonged release of drug from all the formulations with zero order kinetics. The activity of liposome formulation was found to be significantly lowered by the *in vivo* intraocular pressure and sustained for longer period of time which improves its physiological effectiveness. Thus, liposome offer a promising way to fulfil the need for an ophthalmic drug delivery system that not only has the convenience of a drop, but that can be helpful to provide the localize drug action and maintain drug activity at its site of action for a longer period of time and minimizing frequency of drug administration with patient compliance. It prepared an ocular insert of moxifloxacin HCl by using various polymers for controlled drug delivery[27]. The objective of this preparation was to increase contact time, prolong drug release and minimise precorneal loss of drug**.** The ocular inserts were prepared by using gelatine (18% and 20%), a natural biodegradable polymer and glycerine (70% w/w of dry polymer) as a plasticizer. The cross linking was achieved by dipping cut inserts (8 mm diameter) in 10% w/v solution of glutaraldehyde (as a cross linking agent) in isopropyl alcohol (5 ml) for four different time period of 15, 30, 45 and 60 minutes to delay the release of drug from the formulation. Physicochemical properties of the inserts were evaluated like uniformity of thickness, drug content, weight, swelling index and surface pH. It studied the functional activity and development aspects of *N*-acetylcarnosine for the ocular system as revealed by the use of a variety of physiological, biophysical and therapeutic ophthalmic methods[28]. It has been designed for pharmacists and more advanced ophthalmology, optometry and pharmacology researchers who wish to gain a basic understanding of the biological effects of *N*- acetylcarnosine for vision and to share in the excitement of the latest developments in this field. Topics under the consideration include: ophthalmic drug delivery of *N*- acetylcarnosine eye drops; clinical and functional types of activity of the developed and patented *N*-acetylcarnosine lubricant eye drops designed as 1% *N*-acetylcarnosine prodrug of L-carnosine containing a mucoadhesive cellulose-based compound with corneal absorption promoters in a drug delivery system; management of age-related serious or disabling eye diseases in humans with *N*-acetylcarnosine eye drop therapeutic platform (ocular inflammation, age-related macular degeneration, macular dystrophies, ocular manifestations of diabetes, hypertonic retinopathy, primary open angle glaucoma, vitreous lesions); development and molecular mechanisms of ocular therapeutic activities of carnosine derivatives in the visual system [28].

It developed Methyl Cellulose (MC) based thermo-triggered *in-situ* gelling formulations of Ketorolac tromethamine (KT) to enhance its ocular bioavailability[29]. The gelation temperature of 1% w/v MC solution was 60°C. Sodium bicarbonate ($NaHCO_3$) was added to reduce the gelation temperature of MC solution below physiological temperature, i.e., 370°C. The effect of $NaHCO_3$ concentration on the gelation temperature, rheological property and drug release profile of prepared formulations were also evaluated. It was observed that 5% w/v $NaHCO_3$ lowered the gelation temperature below 370°C and the solution was free flowing liquid at 250°C for proper instillation to the eye as drop and provides the sustained drug release profile.

It prepared and evaluated the Niosomes of brimonidine tartrate and certified that niosomes is a significant vesicular carrier system for therapeutic effectiveness as helpful to increase the duration of action and decrease in dose frequency[30]. During evaluation of drug preparation it follows zero order kinetics and show prolong release of drug. The activity of niosome formulation was found to be lowered significantly by the *in vivo* intraocular pressure and sustained for long period of time which encourages its physiological effectiveness. Thus, niosomes offer a promising way to fulfil the need for an ophthalmic drug delivery system that not only has the convenience of a drop, but that can localize and maintain drug activity at its site of action for a longer period of time thus allowing for a sustained action; minimizing frequency of drug administration with patient compliance. Pharmaceutical product development is a crucial task which is directly dependent on its therapeutic objectives [31]

It studied that the poly (lactide-co-glycolide) (PLGA) microspheres serve as carriers for the topical ocular delivery of a peptide drug vancomycin [32].

In this experiment microspheres were prepared by an emulsification/spray-drying technique that can be

proposed as an alternative to the double emulsion method for preparation of peptide-loaded microparticles. The drug encapsulation efficiencies were evaluated that was close to the theoretical values (84.2–99.5%); the average particle size was about 11 mm. The microspheres were able to modulate the *in vitro* drug release of vancomycin with behaviour dependent on their composition: the highest drug content corresponded to the highest release rate. *In vivo* studies were carried out by determining the pharmacokinetic profile of VA in the aqueous humor of rabbits after topical administration of aqueous suspensions of microspheres. High and prolonged VA concentrations and increased AUC values (2-fold) with respect to an aqueous solution of the drug were observed. Increasing the viscosity of the microsphere suspension by addition of a suspending-viscosizing agent (hydroxypropylcellulose) did not produce an increase of the ocular bioavailability. PLGA microspheres can be proposed as a system for ocular delivery of peptide drugs.

It evaluated the Pectin microspheres as ophthalmic carriers for piroxicam[33]. In this they were prepared the microspheres by a spray-drying technique; their morphological characteristics were investigated by scanning electron microscopy (SEM) and their *in vitro* release behaviour was determined at pH 7.0 USP buffer using a flow-through apparatus. Px loaded in the pectin microspheres showed a faster *in vitro* dissolution rate with respect to solid micronized drug. The precorneal retention of fluorescein -loaded microspheres was evaluated *in vivo* in albino rabbits: an aqueous dispersion of fluorescent microspheres showed a significantly increased residence time in the eye (2.5 vs. 0.5 h) then fluorescein solution. Hence, concluded that increased bioavailability. *In vivo* tests in rabbits of dispersions of Px-loaded microspheres also indicated a significant improvement of Px bioavailability in the aqueous humour (2.5-fold) when compared with commercial Px eye drops.

It reported that nanoparticles and microspheres provide the promising drug carriers for ophthalmic applications[34]. A situation in which use of, or exposure to, a violate product is not likely to cause adverse health Consequences[35]. The binding of drugs depends on the physicochemical properties of the drugs and polymer used, as well as of the nano and microparticle material and also on the manufacturing process for these particles. After optimal drug binding to these particles, the ocular bioavailability of a number of drugs is significantly enhanced in comparison to normal aqueous eye drop solutions as increased solubility. Generally, smaller particles are better tolerated by the patients than larger particles (no irritation). For this reason especially nanoparticles may be preferred for long-acting ocular drug delivery systems, although larger microparticles showed slower elimination kinetics from the precorneal compartment.

Figure 1. Schematic diagram of the human Eye

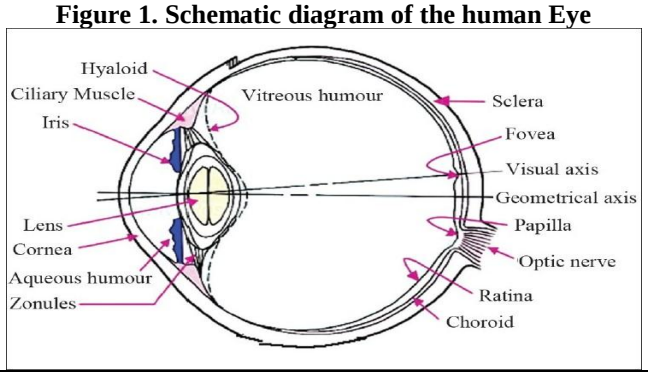

Table 1. Barriers for the Ocular delivery

	Conjunctiva	**Cornea**	**Sclera**
Surface area	17.65 ± 2.12 cm^2	1.04 ± 0.12	16 – 17
Thickness	-	0.57 mm	0.4 -0.5 mm
Structural	Mucus membrane	5 layers	Collagen
composition	Epithelium	Epithelium	fibers
	Vasculature	Bowman's	Water
		membrane	Proteoglycans
		Stomata	Monopolysaccharides
		Descemet's	Elastic fibers
		membrane	Fibroblast
		Endothelium	

Table 2. Commonly Used Fluoroquinolones in Ophthalmic Delivery

Antibiotic generation	Example	Activity
1 st Geneartion	Nalidixic acid	*Have limited activity against gram negative & gram positive organism*
2 nd Generation	Oxolinic acid	Improvement in gram negative coverage including
	Cinoxacin	Antipseudomonal activity.
	Pipemic acid	Shows limited activity against Gram positive organism.
3 rd Generation	Norfloxacin	Having antipseudomonal activity against gram negative bacilli
	Ciprofloxacin	
	Leavofloxacin	
	Ofloxacin	
4 th Generation	Ciprofloxacin	*Having dual mechanism of action in gram positive bacteria in addition*
	Moxifloxacin	reducing efflux from the bacterial cell.
	Gatifloxacin	Improved spectrum of Activity.

CONCLUSION

It can be summarized from whole study that ocular drug delivery system provides a unique carrier system for many pharmaceuticals. Ocular delivery focuses on making formulations more acceptable and excellent drug delivery systems by using the biodegradable and water soluble polymers. It has been found from literature survey that ocular delivery based formulations have great applications for local treatment of eye disease with relatively lesser side effects as compared to other route of drug delivery.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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