NOVEL DEVELOPMENTS IN OCULAR DRUG DELIVERY SYSTEM: A REVIEW

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INTRODUCTION

Eye is one of the most significant and sensitive part of the body. The different layers of tissues are a huge barrier in treating eye diseases, as the structure of the eye is very complex its often find it inconvenient. Ocular drug delivery system is particularly used to fight these complex eye ailments. Recent advancements in pharmaceutical sciences has paved way for new strategies in drug delivery systems. The complex structure of an Eye can be broadly divided into two main parts Anterior segment and Posterior segment. Anterior segment of the eye occupies approximately one-third while the remaining portion is occupied by the posterior segment. Tissues such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make up the anterior portion. Posterior segment or back of the eye include sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor. The anterior and posterior segment of eye is affected by various vision threatening ailments. Diseases affecting Anterior segment include, but not limited to glaucoma, allergic conjunctivitis, anterior uveitis and cataract. While, age-related macular degeneration (AMD) and diabetic retinopathy are the most prevalent diseases affecting posterior segment of the eye.

CONVENTIONAL DRUG DELIVERY SYSTEMS

EYE DROPS

Drugs which are active at eye or eye surface are widely administered in the form of Solutions, Emulsions and Suspensions. Eye drops are largely used only for treating anterior segment disorders as adequate drug concentration are not reached in the Posterior tissues using this drug delivery method. The dose is mostly absorbed to the systemic blood circulation via the conjunctival and nasal blood vessels. But the absorption is limited by corneal epithelium, the maximal ocular absorption is about 10 percent of the dose.

ABSTRACT

Recent advancements in pharmaceutical sciences as paved way for new strategies in Ocular Drug Delivery Systems. Traditionally eye drops was the most convenient dosage form for drug administration, especially for anterior ocular diseases. Delivery of drug to target tissues was restricted by various barriers. Particularly, over the last two decades ocular drug delivery system has seen tremendous research acceleration towards developing novel, safe formulation and drug delivery techniques which will help in delivering drug to targeted tissues. These novel devices and/or formulations may help to surpass ocular barriers and associated side effects with conventional topical drops. Also, these novel devices and/or formulations are easy to formulate, no/negligibly irritating, possess high pre-corneal residence time, sustain the drug release, and enhance ocular bioavailability of therapeutics. An update of current research advancement in ocular drug delivery necessitates and helps drug delivery scientists to modulate their thought process and develop novel and safe drug delivery strategies.

Keywords: Ocular drug delivery systems, anterior ocular diseases and Ocular barriers.
OINTMENTS AND GELS
Sustained release of drug and prolonged contact with external ocular surface can be achieved using ophthalmic ointments but, the major drawback of this dosage form like, blurring of vision and matting of eyelids can limit its use. Pilopine HS gel containing pilocarpine was used to provide sustain action over a period of 24 hours. A number of workers reported that ointments and gels vehicles can prolong the corneal contact time of many drugs administered by topical ocular route, thus prolonging duration of action and enhancing ocular bioavailability of drugs.

OCUSERTS AND LACRISERTS
Ocular insert are sterile preparations that prolong residence time of drug with a controlled release manner and negligible or less affected by nasolacrimal damage. Inserts are available in different varieties depending upon their composition and applications. Lacrisert is a sterile rod shaped device for the treatment of dry eye syndrome and keratitis sicca was introduced by Merck, Sharp and Dohme in 1981. They act by imbibing water from the cornea and conjunctiva and form a hydrophilic film which lubricates the cornea.

EMULSIONS
An emulsion based formulation approach offers an advantage to improve both solubility and bioavailability of drugs. There are two types of emulsions which are commercially exploited as vehicles for active pharmaceuticals oil in water (o/w) and water in oil (w/o) emulsion systems. For opthalmic drug delivery, o/w emulsion is common and widely preferred over w/o system. The reasons include less irritation and better ocular tolerance.

SUSPENSIONS
Suspensions are another class of non-invasive ocular topical drop drug carrier systems. Suspension particles retain in precorneal pocket and thereby improve drug contact time and duration of action relative to drug solution. Duration of drug action for suspension is particle size dependent. Smaller size particle replenishes the drug absorbed into ocular tissues from precorneal pocket.

NOVEL OCULAR DRUG DELIVERY SYSTEM
Nanotechnology based ocular drug delivery
In last few decades, many approaches have been utilized for the treatment of Ocular diseases. Nanotechnology based ophthalmic formulations are one of the approaches which is currently being pursued for both anterior, as well as posterior segment drug delivery. Nanotechnology based systems with an appropriate particle size can be designed to ensure low irritation, adequate bioavailability, and ocular tissue compatibility. Several nanocarriers, such as nanoparticles, nanosuspensions, liposomes, nanomicelles and dendrimers have been developed for ocular drug delivery. Some of them have shown promising results for improving ocular bioavailability.

Advantages of nanotechnology based ocular delivery
- These have quicker onset of action, controls the rate of release, Which protects the drug against agents which cause degradation.
- Increase the residence time.
- Increases the accurate dosing to overcome the side effects.
- Improves bio availability, safety and efficacy.

Nano carriers have capacity to deliver ocular drug to specific target sites. For this purpose different polymers are used. These nano carriers improve their interaction with the corneal and conjunctival epithelia and consequently their bioavailability. The various Nano carriers used for ocular drug delivery system are: Nanomicelles, Nanoparticles, Nanosuspensions, Microemulsions, Liposomes, Dendrimers.

NANOMICELLES
Nanomicelles are the most commonly used carrier systems to formulate therapeutic agents in to clear aqueous solutions. In general, these nanomicelles are made with amphphilic molecules. Currently, tremendous interest is being shown towards development of nanomicellar formulation based technology for ocular drug delivery. The reasons may be attributed due to their high drug encapsulation capability, ease of preparation, small size, and hydrophilic nanomicellar corona generating aqueous solution.

method of preparation
Generally, Nanomicelles are prepared by various methods which are divided into two major groups including, direct dissolution and dialysis methods. These two classes of drug encapsulating procedures depend primarily on the physicochemical properties of the block copolymers. Particularly, the choice of the appropriate method is typically based on the extent of the solubility of a micelle-forming block co-polymer in an aqueous medium.
Direct dissolution method is the frequently employed method for micelle preparation from copolymers with relatively high water solubility. This method involves dissolving the drug and the block copolymer directly in an aqueous medium (distilled deionized water or buffer). Method of preparation may require stirring, heating and/or sonication in order to load drug into nanomicelles. This method has been generally employed for moderately hydrophobic polymers such as poloxamers and also to formulate polyion complex micelles (PICM) with a slight modification. The dialysis method is frequently employed for micelle preparation from amphiphilic copolymers with low water solubility. For this method, the copolymer and the active agent are dissolved in a common organic solvent and micelle formation is stimulated by the addition of aqueous medium (water) to the drug-copolymer mixture. The micelles are subsequently dialyzed against water for an extended time periods to eliminate organic solvent. Moreover, the selection of the solvent significantly influences the physical and drug encapsulation properties of the micelles. Another method commonly employed is the dry-down or evaporation method wherein both the copolymer and active agent are dissolved in a common solvent or mixture of two miscible solvents.

NANO SUSPENSION
Nano suspensions had a quicker onset of action and enhanced dose proportionally, nano suspension also alter the pharmacokinetic parameters, improve the safety and efficiency of the drug. Nanosuspensions consist of poorly water soluble drugs, suspended in an appropriate dispersion medium. Nanosuspension technology can be better utilized for drug compounds that form crystals with high energy content, which renders them insoluble in either organic (lipophilic) or hydrophilic media. Polymeric nanoparticle suspensions, which are prepared from inert polymeric resins, can be utilized as important drug delivery vehicles, capable of prolonging drug release and enhancing bioavailability. Since these carriers do not irritate cornea, iris or conjunctiva, they act as an inert carrier for ophthalmic drugs. Nanosuspensions can also be used to achieve sustained release of the drug by incorporating or formulating with suitable hydrogel or mucoadhesive base or in ocular inserts. Flurbiprofen (FLU) loaded in polymeric nanoparticle suspensions, prepared from Eudragit RS 1001 and RL 1001 polymers are reported to prevent myosis induced during extra capsular cataract surgery.

Method of preparation
Preparation of nanosuspensions, mostly two methods namely “Bottom up technology” and “Top down technology” are used. Bottom up technology is an assembling method to form nanoparticles like precipitation, microemulsion, melt emulsification method and top down technology involves the disintegration of larger particles into nanoparticles, examples of which are high-pressure homogenization and milling methods.

Microemulsion
Microemulsion were first described Hoar and Schulman. Microemulsion is a dispersion of water and oil that formulated with surfactants and co-surfactants in order to stabilize the surface tension of emulsion. Microemulsion have a transparent appearance, with thermodynamic stability and a small droplet size in the dispersed phase (aqueous and nonaqueous phase) (<1.0μm). Microemulsions are an interesting alternative to ophthalmic formulation, due to their intrinsic properties and specific structure. They can be easily prepared through emulsification method, easily sterilized, and are more stable and have a high capacity for dissolving drugs. The ophthalmic o/w Microemulsion could be advantageous over other formulation, because the presence of surfactants and co-surfactants increase the drug molecules permeability, thereby increasing bioavailability of drugs. In 2002 the FDA approved the clinical use of an anionic emulsion containing cyclosporine A 0.05% for the treatment of chronic dry eye. non-medicated anionic emulsion for eye lubricating purposes, in patients suffering from moderate to severe dry eye syndrome (Refresh Dry Eye Therapy, Allergen), and two lipidic emulsions, indicated for the restoration of the lipid layer of the lacrimal fluid (Lipimix, Tubilux Pharma, and Soothe XP Emollient Bausch and Lomb). The cationic nanoemulsions such as the product Cationorm (Novagali Pharma, France) was launched in the European market for the treatment of dry eye symptoms.

Method of preparation
Phase titration is low-energy emulsification method. This utilizes the spontaneous diffusion of surfactant or solvent molecules into the continuous phase due to ultra low interfacial tension. Preparation of ME involves investigation of area of formation of single-phase region in the phase diagram which is composed of 4 corners, each of oil, water, surfactant, and cosurfactant,
respectively. In this method, all the components of formulation are mixed in proportions varying from 0 to 100% representing in the phase diagram, in anticipation to obtain a clear phase. Subsequently, optimization is appropriately done based on the most clear region in the phase diagram and then to finalize the composition of most stable.

NANO-CRYSTALS
Nano-crystals are nanoparticles, being composed of 100% drug without any matrix material, typically with a size range between 200 and 500 nm. Several methods are used to reduce the particle size of a drug—that is, bottom-up and top down technologies. The striking advantage is that the drug nano-crystals can be applied by various administration routes, including ophthalmic administration, to create systems with prolonged retention times; moreover, they constitute a simple system—simple to produce and simple to use. Currently there are few studies investigating NSAIDs in the form of nano-crystals for ophthalmic application, because the major prerequisite for nanocrystal formulation is the hardness of the drug crystals. The striking advantage is that the drug nano-crystals can be applied by various administration routes, including ophthalmic administration, to create systems with prolonged retention times.

method of preparation
Several preparation methods for drug nanocrystals have been investigated. The techniques to produce drug nanocrystals can be divided in two basic approaches, namely the bottom up and the top down technologies. To obtain nanoparticles of drugs, the top down processes involve a breaking down of larger particles by milling or homogenization, while the bottom up processes associate with an assembling and controlling of precipitations at nanometer scale.

DENDRIMERS
Dendrimers are macromolecular compounds made up of a series of branches around an inner core. They are attractive systems for drug delivery because of their nanometre range, ease of preparation and functionalization, and their ability to display multiple copies of surface groups for biological recognition processes. Because of these properties, they can be used as an effective vehicle for ophthalmic drug delivery. The use of bioadhesive polymers, such as poly (acrylic) acids, to improve drug delivery and release by optimizing contact with the absorbing area in order to prolong residence time and decrease dosage frequency. These bio-adhesive polymers, however, are associated with problems like blurred vision and formation of a veil in the corneal area, leading to loss of eyesight. To avoid these problems, dendrimers like poly (amidoamine) (PAMAM) are used.

method of preparation
- Divergent growth method
- Convergent growth method
- Hyper cores & branched monomers growth
- Double exponential growth

First two methods are mainly used for the synthesis of dendrimers.

Divergent growth method
In this method growth of dendrimer originates from a core site. The core is reacted with two or more moles of reagent containing at least two protecting branching sites, follows by removal of the protecting groups, lead to the first generation dendrimers of the described size is obtained. By this approach the first synthesized Dendrimers were polyamidoamine (PAMAM) also known as ‘star bust Dendrimers.’

Convergent Dendrimer Growth Method
Divergent method is an ‘inward to outward approach whereas convergent approach is ‘outward to inward’ approach. It starts with synthesis of dendrimer branches separately and then connecting them to the initiator core. The branches are synthesized separately and finally joined to the core to produce dendrimer.

For each category of Novel Systems, these are research works done previously.
Nanomicelles
1. The title of the article is “Controlled ocular drug delivery with Nanomicelles” by Ravi D, Varun Khurana, Sulabh Patel, and Ashim K Mitra. In this article, anatomy of eye and various routes of administration were explained. And about nanomicelles, types of nanomicelles and methods of preparation. And there release profile, pharmacokinetic parameters are explained.
2. “Novel Nanomicelles formulation approaches for anterior and posterior segment ocular drug delivery system” by Kishore Cholkar, Ashaben Patel, Ashwini Dutta Vadlapudi and Ashim K Mitra. In this, segments of the eye, types of nanomicelles and methods of preparations were explained. Micelles in anterior and posterior segment ocular drug delivery were explained. And their pharmacokinetic parameters and there evaluation studies were explained. And also current and future developments were discussed.
3. Title of the article is “A review on impact of Nanomicelles for ocular drug delivery system” by Pawan Singh and Navneet Verma. In this article anatomy of eye and classification of nanomicelles, drug absorption in the eye, its advantages and disadvantages of nanomicelles.

Nanosuspensions
1. Nanosuspension Drug Delivery System – (An Overview) by Sahilhusen I Jethara, Mukesh R Patel and Alpesh D Patel. In this, importance of nanosuspension, its advantages and disadvantages, methods of preparation like top-down and bottom-up method. And evaluation studies like invitro and invivo are explained.
2. “Nanosuspension : Potential applications of nano therapeutics in ocular drug delivery” by Payghan SA, Nangare KA, Kate VK, Pawar SD and Khavane KK. In this article considerations of nanosuspensions for ocular drug delivery was explained briefly. Ocular drug delivery mechanism, its barriers and strategies to overcome blood ocular barriers were explained. And applications of nanosuspension in ocular delivery. In conclusion they have concluded that nanosuspension formulation solves the poorly soluble drugs in order to achieve bioavailability, dissolution velocity and bio-adhesion of the drug.

Microemulsions
1. “Microemulsion: a potential novel drug delivery system” by Jaspreet Kaur Saini, Ujjwal Nautiyal, Senthil Kumar, Devendra Singh, Firoj Anwar. Components of microemulsions and classification of microemulsion are explained. Methods of preparations, a) Phase inversion method and b)Phase titration method. Characterisation of microemulsions and research work on microemulsion was also explained. In conclusion microemulsions have been shown to be able to protect labile drug, controlled drug release increased drug solubility, increased bioavailability, reduce patient variability and increase the rate of absorption.
2. “Delivery of Gatifloxacin using microemulsion as vehicle: formulation, evaluation, transcorneal permeation and aqueous humor drug determination” by Md Abdul Kalam, Ibrahim A Aljuiffali, Anil k mitra and Yasmin Sultan. In this article, importance of microemulsions, materials like Gatifloxacin, Tween80, diethylene glycol monoethylether, dialysis membrane are used to prepare microemulsions. And its evolution studies like invitro drug release are explained.

Nanocrystals
1. Title of the article is “Nanocrystals for ocular drug delivery system” by Om Prakash Sharma, Viral Patel, Tejal Mehta. The complexity of the structure and nature of the eye is explained. Nanocrystal based formulation explored for ocular drug delivery have been found successfully in achieving increase in retention time, bioavailability and permeability of drugs across the corneal and conjunctival epithelium. The perspectives of nanocrystals as an emerging flipside to explore the frontiers of ocular drug delivery are discussed.
2. “Nanocrystals for enhancement of oral bioavailability of poorly water soluble drugs”. Special features of nanocrystals to enhance oral bioavailability, increase in saturation solubility, increase in dissolution velocity, increase in adhesiveness to surface/cell membrane. Preparation of nanocrystals, milling or homogenisation. And evaluation studies like invitro drug release is explained. In conclusion, the surface modification of nanocrystals effects the absorption pattern and determines the cellular affinity. This aspects of nanocrystal can be employed as the new approach for the targeted delivery.

Dendrimers
1. “Dendimeric systems and here applications in ocular drug delivery” by Burcin Yavuz, Sibel Bozdag Pehlivan and Nursen Unlu. In this article, importance of nanotechnology and about dendrimers if explained. Permeability properties of dendrimers and there structures, synthesis, properties and types dendrimers. Interactions between dendrimers and drug molecules, encapsulations of drugs with in dendritic structure. And also ocular applyof dendremeric drug delivery system were explained.
2. “Dendrimers as drug carriers: applications in different route of drug administration” by Yiyun Cheng, Zhenhua Xu, Minglu MA, Tongwen Xu. In this, importance of dendrimers structured synthesis and properties of dendrimers, interactions between dendrimers and drug molecules and applications in different routes of drug administration were explained.

CONCLUSION
As the drug delivery to Posterior segment still remains to be a big challenge. Topical application is not yet promising and this problems could be addressed by novel ocular drug delivery systems which are developed with integration of biomedical engineering and nanotechnology. Drug delivery by topical and Intravitreal routes cannot be considered safe, effective. In recent years, scientists have focused on designing a strategy with a multidisciplinary approach e.g. micro needles, microemulsions, nanosuspensions, iontophoresis and MRI. Until then present methods of drug delivery can cater the need of treatment to sight treating Posterior segment of Eye. Further research is required in the field to optimize drug formulation deliver to targeted tissue, this will enhance the drug delivery and minimize adverse effect.
REFERENCE

[2] [www.ncbi.nlm.nih.gov/pmc/articles/PMC4289909](www.ncbi.nlm.nih.gov/pmc/articles/PMC4289909)
[14] Shek PN, Barber RF, Liposomes are effective carriers for the ocular drug delivery of prophylactics, Biochem, Biophysics Acts.