A REVIEW ON CHITOSAN BASED NANOPARTICLE AS A NEW OCULAR DRUG DELIVERY

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Summary

A new investigation on the chitosan based nanoparticles for the drug delivery to the ocular surface has been launched. The best example model taken is cyclosporine A duely because of its potential activity for the treatment if the local ocular diseases.chitosan has a low toxicity and good ocular tolerance. It also shows the activities of bioadhesion and permeability enhancing properties. These chitosan based nanoparticles act like the transmucosal drug carriers. They transport the drugs to the inner eye. the interaction of these chitosan nanoparticles can be well studied in vivo and invitro conditions using variety of techniques, of which a unique method in which CsNP's are labeled with fluoriscein isothiocyanate-bovine serum albumin produced by the inotropic gelation .later a technique used the liposome-chitosan nanoparticles by a formation of complex between the liposome and chitosan and chitosan nanoparticles .A nano carrier can carry an active molecule which interacts with certain specific ocular structures. These overcome the ocular barriers. Another important character of these particles being able to prolong their residence time in the target tissue.

Key word; Chitosan, Nanoparticals, ocular diseases, biocompatibility, ocular drug delivery,

Introduction

In the present day scenario there are various methods employed to treat ocular diseases. All these applications require to maintain the drug in appropriate effective levels at the site of action for a prolong period of time to achieve a good pharmacological response.[1] Ophthalmic drug delivery is benefited by the use of nanotechnology based drug delivery system[2].There i s another major disease called diabetic retinopathy(DR) which is chronic disease and affects almost about 60-75% of the total diabetic population[3].There is retinal neuronal loss and an increase vascular permeability in the early stages of diabetics .The insulin therapy would reduce the retinal neural apoptosis in diabetic rats. Insulin therefore helps the retinal neurons from cell death in a phosphatidyl inosital 3-kinase Nonetheless the dependent fashion[4].The intraocular injection of insulin restores the basal retinal insulin receptors activity in diabetic rats[5].There need to be local delivery of insulin to the retina for a longer period of time.There area several ways through which these drugs can be delivered to the retina may be by systemic or topical ,subconjunctival or intravitreal routes[6-9].The drug delivery to the eye-retina is difficult task as it has a limited access to the retina and blood ocular barriers. There are also certain other types of deliveries of drugs like the intravenous or orally .However there is a risk of acquiring systemic toxicity. The topical administration may be effective for ocular anterior segment. It has various barriers for the corneal epithelium. Intravitreal administration is an effective means of delivery therapeutic levels of drug. There are also minimum systemic side effect[10-12] .The nanoparticles as the carriers for ocular drug delivery is mainly because of their capacity to protect the encapsulated molecule during its transport to various compartments of the eye[13-19]furthermore nanoparticles play a significant role in the field of new gene therapies for treatment of ocular diseases[20,21,70]

Since past two decades scientists have put their efforts to the overall development of nanocarriers' ocular drug delivery systems. This effort has made to put forth during the time of hydrophobic nanoparticles which consists of polyalkylcyano acylate [22-24].Also the polyesters namely e-caprolactone [25-27] later a conclusion was drawn that the nanoparticles have an affinity towards corneal epithelium. But they accumulate in the mucosal epithelium .As a result we worked out on nanoparticles with hydrophilic coating to increase its stability and their interaction with mucosa. [28, 29].polyethylene glycol (Peg) and chitosan are the two basic natural polymers used. These two materials have their own significant role. The role played by (PEG) is the protein rejection and chitosan acts like a cationic polysaccharides[28,29]

. Retinoblastoma is third most common form of cancer in infants and is an ocular disease that requires attention as in approximately 90% cases metastatic retinoblastoma is lethal. This situation usually arises in children living in developing countries the cause being poor education, lower socio-economic status and inadequate healthcare systems which delays diagnosis and suboptimal care [30]. More recent treatment options for retinoblastoma include the external beam radiotherapy,episcleral plaque radiotherapy and cyrotherapy.[31].Moreover blood-retinal barrier also limits the potential of various anticancer agents[32,33].encapsulation of cytotoxic drugs in nanoparticles could help to reduce side-effects and increases the therapeutic index. they would also help in retention and penetration problems of the blood-retina barrier[32,33].Although it has been shown that poly(alkylcyanoacrylate) poly_e caprolactone nanoparticles are able to improve the intraocular penetration of the drugs their lifetime of these drugs on the ocular surface remains for few hours[34].

The topical drugs for ocular surface are given in the form of eyedrops.As a result the bioavailability of the physiological properties such as tear turn over and the blinking reflex.[35,36].It is evident that the best way to absorption of drugs into the eye requires the corneal penetration and prolonged contact time with the corneal epitheliums [36-38].Polyvinyl alcohol PVA a water soluble polymer is usually used due to its mechanical strength, biocompatibility and the non toxicity nature[39].Therefore it is used as one of the ingredients for the ocular such as the eye drops.[40-42] ocular solutions and suspensions[43].Sodium carboxymethyl cellulose is another important naturally occurring polymer which has a good biocompatibility [44].It also acts as a viscosity enhancing agent in various eye drops.[45].

Poloxamers polymers for the ocular drug delivery:

Ciprofloxacin is another broad spectrum fluoroquinoline antibiotic used in ophthalmology for the treatment of blepharitis,conjunctivitis and bacterial keratisis which is caused by staphylococcus aureus.It is used in the treatment and prevention of corneal ulcer and endophthalmitis.Fluoroquinolines are also used in the treatment of other skin diseases.[46,47]

The best suited drugs for the ocular treatment must contain the property of localized action such as the eye drop solution. There is a shirt precorneal contact ion time coupled with the corneal impermeability will result in the low bioavailability of the drug and as a result frequent dosing is required.[48].The drugs must avoid the rapid dilution and for that they must have an increased viscosity.[49].Thermo sensitive amphiphilic copolymers namely poly(ethylene oxide) poly (propylene oxide)-poly(ethylene oxide) are extensively used under investigated as in situ for gelation.[50-54].The interaction between the different segments of the copolymers will explain the thermogelification of poloxamers which is the most accepted mechanism.[55-56].The poloxamers polymers aggregate into micelles.these micelles are spherical with dehydrated polyoxypropylene(pop)chains[58].An increase in temperature causes dehydration and conformational changes at the hydrophobic chain regions increases the chain sequence and the entanglement of the network[59,60].More unbound water is available at the hydrophilic regions in the gel[61].At the point where gelation has occurred and apparently intact and orderly compact [which is called as "hard-sphere crystallization".[62].poloxamers suffer from a property of weak mechanical strength which leads to rapid rosions.Another important aspect is the combination of poloxamers with the other polymers like the carbopol[63] and alginate[64].Carbopol is a mucoadhesive polymer which increases the mechanical strength and also the contact time.Carbopol shows the a solid to gel transition at a ph range of about 5.5.To have no problem the ph is made acidic before carbopol phase transition .This formulation would stimulate the eye tissue to increase the lacrimal secretion and blinking reflex as a result drains the drug easily.[64].

. chitosan is an excellent biodegradable polymer for the ocular compatibility.[65-67].It presents positively charged amine groups in its chemical structure that could interact with the negatively charged mucous layer which conferring mucoadhesive characteristic.[68,69].These chitosan particles have the prolonged contact time with the ocular surface as a result when mixed with the poloxamer would be the most promising for ocular therapy.[68]Infect specific blend of poloxamers and chitosan for ocular delivery of timolol maleate were already studied.[67].It was found that these polymers can be produced in combination to produce clear sterile and non-irritating ophthalmic formulations[69].Nonetheless the chitosan and the polymer concentration used was very less .Chitosan was not used to improve the mucoadhesive properties and mechanical strength. The determination of the mechanical strength and the mucoadhesive properties of the polymers with respect to the chitosan were not performed in vivo. Therefore the

methods that could make the topical treatment for the ocular diseases feasible. Hence the aim of developing an improved methods of ophthalmic delivery in which an improved mucoadhesive properties and the mechanical strength were studied. Therefore to reach such expectations poloxamer and chitosan were used to prepare insitu forming gels. The former is used as the gelling agent and the later is used as a mucoadhesive agent. The rheological and mechanical properties, as well as the mucoadhesive ability of the poloxamer gels as a function of chitosan concentration, were evaluated. These results were used as a screening process to select
The most suitable polymer concentration for the in vivo studies, where gamma scintigraphy was used in human eyes to evaluate the retention time of the Formulation.[knauer,Berlin,Germany].

Conujunctival and the sub-conjunctival application:

The conjunctiva is a thin transparent mucous epithelial layer of the which lines the inside of the eyelids. It almost covers one-third of the anterior eye balls. The conjunctiva has two layers namely the outer epithelium and the inner underlying stoma. The epithelium consists of stratified epithelial cells and the microvilli.The exposed surface of the eye is the conjunctiva and the corneal which are protected by the tear film by secreting mucin,.electrolytes and fluid.Topically applied drugs reach the intraocular region of the eye, either by corneal or the non-corneal pathways. In animals the amount of lipophilic drugs in the iris–ciliary bodies which is absorbed by the corneal and non-corneal has a ratio of 70:1 for hydrocortisone.By contrast insulin a hydrophilic model drug with a molecular weight ~5000Da is absorbed primarily by the by non corneal pathways as conjunctiva is more permeable to the hydrophilic solutes than the cornea .Conjuctival-scleral pathways is favored for the delivery of hydrophilic drug.Para cellular delivery of hydrophilic solutes across the conjunctiva may rather be limited since the conjuctival epithelial cells are joined by tight junctions at the apical most aspect of the epithelium. These junctions form the barriers between adjacent cells and act as a major cause for diffusion of the drugs from the Para cellular pathways.The conjunctiva may allow the permeation of the hydrophilic drugs with the molecular weights of ~20,000 whereas cornea is not permeable to insulin and FD20.Although in vivo approach to study the transport of drugs from ocular to intraocular surface tissues under certain physiological conditions using rabbits and rats by topical application of the drugs and assess the absorption capacity of the conjunctiva and cornea are being studied by many laboratories..There are several active transport mechanisms like the secondary active solute transport,d-glicose transport, lipid transport, amino acids transport.Although several issues have appeared for the intraocular delivery by the conjuctival pathways, we challenged to investigate for the delivery of drugs to the posterior area of the eye. We have found that nipradilol,a beta blocker and iganidipine,ca^{+} antagonist are good examples to reach the posterior segment of the eye of monkey and the rabbit although the mechanism of the transport is not known. To overcome this problem of transport mechanisms several defense mechanisms have come up.

Passive transport of the drugs to conjunctiva:

Improving the drug delivery to the conjunctival region is one of the challenging task in the ocular drug delivery. In the past efforts have been put forward on either enhancing the transcellular drug penetration by increasing the drug lipophilicity through the use of prodrugs or analogs or improving the paracellular penetration by using enhancers to open tight junction.Apparently the lipophilic drugs are better absorbed than the hydrophilic drugs via transcellular route. A lipophlc drug proponalol with a log partition of octanol and water of 3.21 is absorbed through the cornea and the conjunctiva 5-1 fold greater than the hydrophilic drug sotalol.The penetration of the beta blockers through the conjunctiva is increased by its lipophilicity with a sigmoidal relation..Peptide and protein drug delivery studies have been made by the pharmacists to use as an alternate route for the administration of parenteral route .Peptide and protein drugs are thought to be transported across the ocular routes in part via paracellular pathways due to their hydrophilic nature.Paracellular pathways of epithelial barriers like the cornea and conjunctiva are where the neighbouring cells are held together at the apical aspects by the tight junctions,which acta s a rate-limiting step for diffusion of macromolecule drugs including proteins and peptides.There is an equivalent pore that suggests that the conjunctiva may allow the permeation of hydrophilic substances eitha molecular weight ~20,000 and the equivalent pore radius is 5.5n[(68)]

The role of nanoparticles in the drug delivery of corneal transplantation:

There is another important criteria namely the corneal transplantation in which majority of them serve to graft rejection and approximately about 90% of the individuals are undergoing this problem. Immune graft rejection seems to be the actual cause for it[Xie et al ,2002].Even though several nanoparticle materials Like the cyclosporine [milani et al] and rapamycin (RAPA)[Dong et al, 2005] which act as the immunosuppressive agents. It is also noted that several experiments were conducted which uses cyA polylactide – co –glycolide as the polymer implant which was induced into the rat anterior corneal region. However the most convenient method for the intraocular administration will be the topical application, as it has an improved patience compliance.

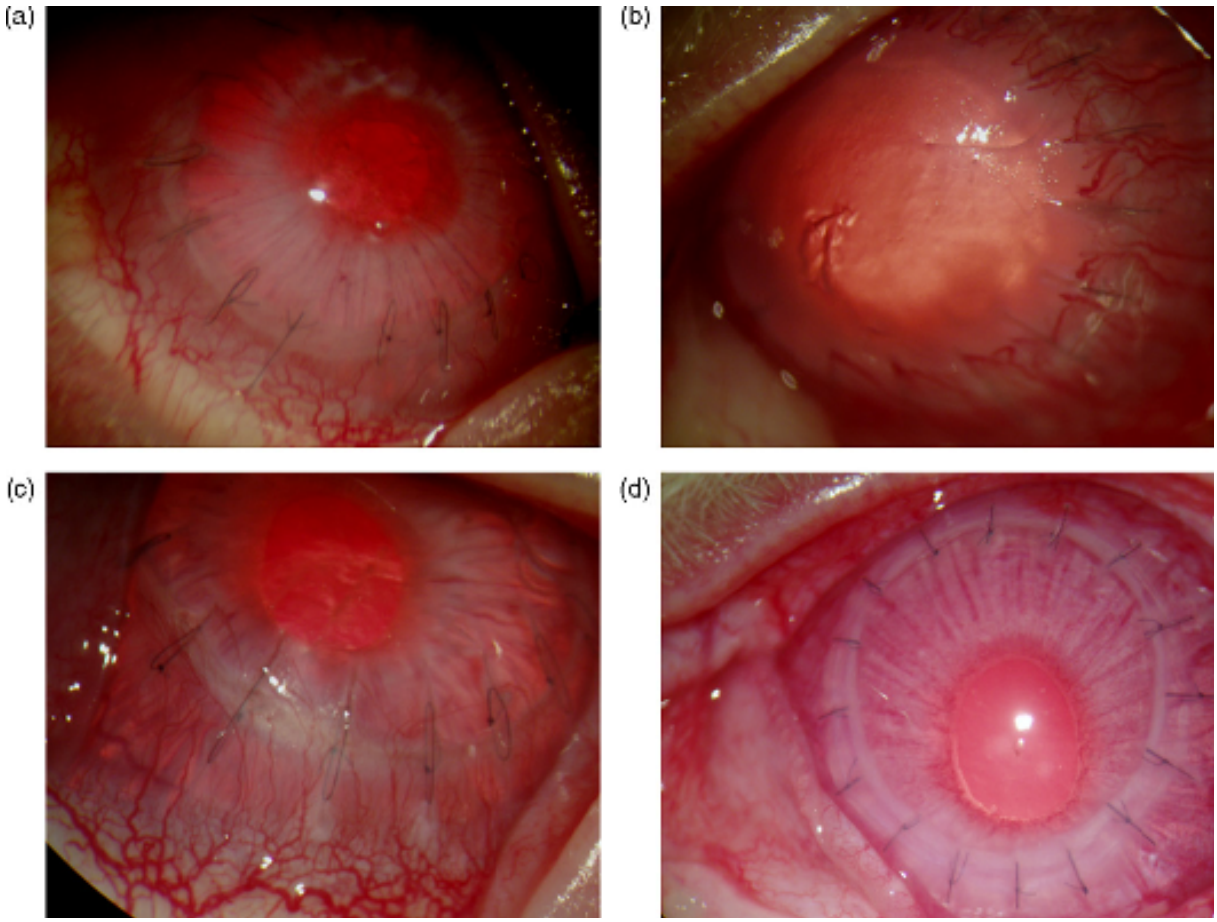


Fig. 5. Recipients of corneal allografts observed by slit lamp microscope 10 days after transplantation. (a) Control group, (b) empty particles RAPA group, group, (c) and (d) RAPA-particles group

Among several new discoveries the polymer which has gained the attraction was the cationic chitosan (CS) because it has an excellent biocompatibility and the biodegradability.[Hirano et al.,1999;knapczyk et al .,1984]. The nanoparticles which are coated with the CS and which have the capacity to crosslink themselves ionically are intended to have a greater retention time on the ocular surface of the cornea by the topical administration [calvo et al., 1997; genta et al., 1997; Decampos et al., 2001].There is a thorough investigation on the immunosuppressive RAPA as the agent used in the corneal transplantation. For this purpose RAPA is loaded with the CS/polylactic (PLA).They are topically applied to the cornea of the rabbit. Several experiments conducted on this aspect using cholesterol and chitosan (CS-CH).These cholesterol chitosan are hydrophobic ally modified. So these nanoparticles are loaded into CyA and used as the carrier for the corneal transplantation [Yuan et al., 2006]

. Cyclosporin A is the agent which acts like a undecapeptide.It plays a unique role in the transplantation of the organs, as it is the immunosuppressant. There is an inhibition of the interleukin 2 release during the activation of the T-cells and therefore causes the suppression of cell mediated immunity..About 25-75% of the CsA concentration was measured in the tears when approximately 5% mg/kg was administered orally but it has an adverse effects of

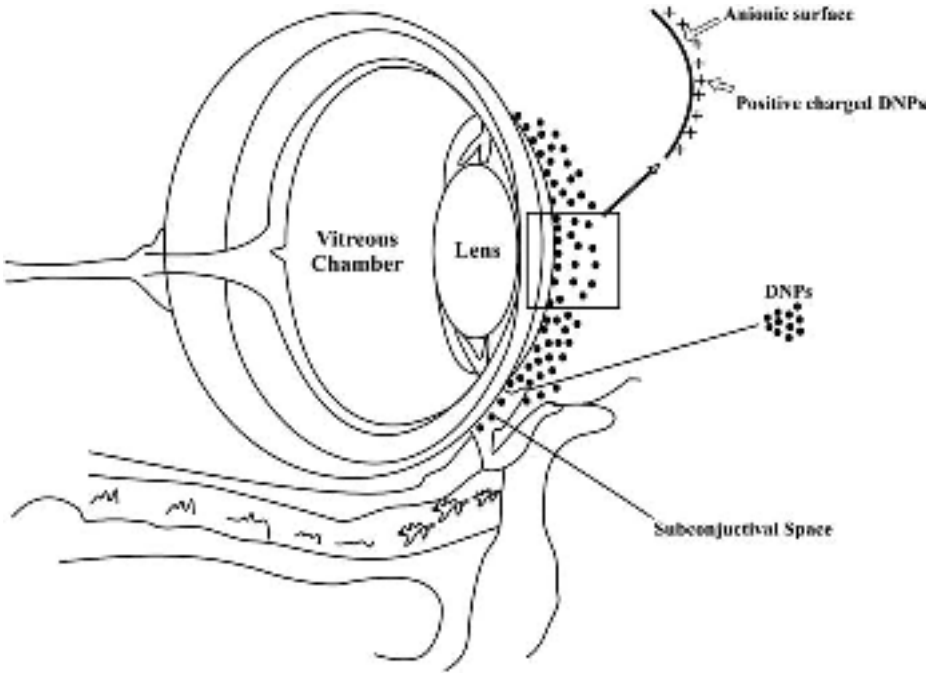
nephrotoxicity and hypertension.CsA is a potential drug which plays a major role in the ophthalmology and treats several intraocular inflammations CsA is used to treat several diseases like the vernal conjunctivitis when administered topically despite of its poor intraocular penetration.Most of the drugs are applied to the eye n the form of topical route. This route is mainly preferred due to its easy administration and maintains a good therapeutic effect. The administration of these drugs by the CsA is beneficial as it reaches mainly the anterior part of the ocular surface and also to the intraocular region of the eye.Another interesting aspect is that CsA mixed with the peanut oil showed the non-toxic effect in the rabbit cornea. However the corneal surface toxicity was not yet well established. The drugs for the topical administration requires certain vehicles like the camphor called as petrolatum oils and the ointments .certain oils like the olive oil,castor,peanut are used to solubulise the CsA.From the assumptions made by certain authors show that the oils cannot be tolerated by the eye due to their lipophlicity.A detailed studies were carried on the solubility of certain agents like the CsA.Cyclodextrins are the complex sugars of cyclo-Malto-hexose which contains the hydrophilic and the hydrophobic layers.Due to the physiochemical characteristics the cyclodextrins will enable them to attach themselves to the lipophilic agents and this increases the solubility of these agents. This can be shown by the combination of CsA with the cyclodextrins which increases the solubility up to 750 mg/ml.Azone is used as the penetration enhancer as it increases the solubility of the drug along with the CsA.They slightly modify the corneal epithelium and this leads to the penetration of the drug into the eye.The Azone in CsA has caused a decrease in the tissue rejection's he enhancer has also caused a corneal cytoxicity.There are certain colloidal carriers like the suspensions, emulsions ,nanoparticles ,nanosperes and naocapsules. Which act as the carriers and are stored in the epithelial cells of the cornea and they will slowly release the drug particles to the site of action shown by calvo.These act as the reservoirs ..Emulsions are another colloidal agents in drugs for example the oil in water emulsions like the castor oil in water will have a lipophilic property as a result they can be well used in the delivery of the topical drugs to the eye.The ultimate aim is to prolong the retention time of the drug in the corneal or the ocular surface. The epithelial corneal cells have a negative charge on their surface, Klang has hypothesized that the emulsions with the positive charge and due to this the retentions time is increased on the ocular surface..Any charge producing agents like the strearylamine could be used in order to improve the penetration of the drugs to the intraocular region.A variety of nanoparticles have been employed especially for the i.v route. As we are aware of the advantages provided by the nanoparticles like the biocompatibility, greater retention time on the corneal uptake, improved tolerance, enzymatic degradation. The important study made is on CsA loaded nanoparticles by calvo and his coworkers. According to their studies nanocapsules made were composed of the oily phase with the a poly (caprolactone) coat..The CsA loaded particles with the polymers like poly(acrylic) acid carbopol,poly(isobutylcyanoacrylate) have been used in the bovine corneas.[(69)]

A colloidal suspension of the DNP's for the ocular surface drug delivery:

Now-a –days better applications for the eye disease are being discussed like the colloidal systems in the drug delivery. The eye ointment would create a discomfort when they are applied. Hence forth the systems are implemented which can avoid the discomforts caused by the ointments as these agents will cause the blurred vision when applied onto to the eye. The colloidal carriers such as the nanoparticles and the liposome's are used to overcome this

problem. But difficulty arises with the liposome's carrying the positive charge on the ocular surface. Because the positively charged liposome's are preferentially attracted at the negative sites of the corneal surface than the ones with the negative or neutral liposome's.To attain a sustained release and the prolonged therapeutic activity the polymers must remain in the ocular cul-de-sac after the topical administration. This will help the drug to release in a sustained mode of drug delivery and would slowly release the drug particles from the nanoparticles.If the drug is released too slowly or too fast then there is a possibility for the drug to come out or lashes out of the eye through tears and the concentration of the drug in the eye will be too low. This causes the drug to penetrate into the intraocular regions .An interesting aspect of using nanoparticles is that the larger particles would create the feeling to scratch. As the size is large.DNP's which act as the carriers and the bimolecular using the nanoparticles the PLGA,PLA, albumin,chitosan can improve the drug delivery to the ocular region in many animal cultures.The chitosan have been described as the best mucoadhesive cationic polypeptide.The polymeric nanoparticles used for the ocular drug delivery as the colloidal systems utilizes the aqueous solutions. The nanoparticles are finely fabricated for the bioactivity . These fabrication of the polymers is done by salvation evaporation, diffusion –emulsification, salting out .But certain limitations like the timolol eye drops have the very side effects such as bradychardia, hypertension and bronchial asthma

DNP's are also used for a multiple tasks such as the uptake of poorly permeable drugs by the ocular epithilia, reduced cellular and tissue clearance of the drug.Nanoparticles can be targeted to the organs such as the spleen,liver,lung and the bronchia as these are very small and can penetrate the narrow bronchioles. They can also be in the blood for a prolonged period of time. As they experience the least phagocytosis.



The DNP's interaction on the ocular surface and conjunctival space of the eye

A recent advancement in the ocular drug delivery:

Recently an advancement has been attained in using the bioinorganic hybrid material for the drug delivery[Li et al.,2010].Layered double hydroxides (LDH'S) or the anionic clays which act as the two dimensional lamellar with the positively charged layers and charge balancing anions in the inner layers. The novel advanced search has helped to improve the synthesis of a large range of these LDH's.The best method to prepare these are the direct method like coprecpitation and the indirect method like the anionic exchange using LDH's as the precursors.[laadewig et al .,2010].The LDH like the Al-Mg and Ni-Al are used[weir and kydd.,1998].And considering the pH range of about for the ocular drug delivery will be 5.0-9.0 and the commercially available diclofenac ophthalmic solution lies between 7.0-7.3[Ahuja.,2006].

NSAID's in the ocular therapy

This is another interesting topic to study about the anti-inflammatory drugs acting on the eye. Ocular inflammation is the common problem faced by the patients undergone the cataract surgery having severe pain and photophobia which leads to the complications like increased intraocular pressure and edema.Non-steroidal anti-inflammatory drugs are a class of compounds which do not contain the steroidal center or the nucleus which are derived from cholesterol biosynthetically in their chemical structure. Also called the COX inhibitors, based on their activity the NSAID's are important In the ocular therapy .The importance of NSAID's has increased in the recent years as they overcome certain defects like the cataract formation and low therapeutic effect at the site of the target.[.Recently the administration of NSAID's has been recommended in the postsurgerical operation of cataract by the U.S drug and food Administration.

N-trimethylated chitosan for trans and precorneal drug delivery:

It is very intresting to know that the best acting chitosan hydrogels are in its deacylated Chitin .Chitosan acts as a good transmucosal absorption of the eye but whereas it has a limitation that it does not work at a neutral pH of the tear fluid.This can overcome by the use of N-trimethylchitosan chloride(TMC) which can act without the pH variability.TMC can increase the permeability of hydrophilic molecules.TMC can be prepared from the crab shells.The deacylation and the molecular weight of the chitosan molecules can be determined by the IR spectroscopy .TMC was synthesized by two reductive methylation steps.Chitosan is found as the chitosan hydrochloride commercially in the market. The tendency of each drug to interact in solution with the PEO–TMC polymer system was been investigated based on the dialysis technique.There is a rapid and reproducible method for the preparation of TMC microspheres loaded with predetermined drug weight fractions.The invitro studies of Dexamethasone or tobramycin as a drug and conducted experiments which compare the PEO based inserts having the TMC microspheres and the ones with TMC-free inserts.This has served us the importance of TMC based inserts for the transcorneal penetration for the invivo studies .As the invivo and the invitro studies of the TMc results should not be similar and there is an absence of TMC effects on the invitro release mechanism.It was also observed that the rate showed a similar absence on the in vivo.

Conclusion:

As we are moving towards the 20th century several studies and applications have been improvised in the case of using nanoparticles in the controlled drug release for ocular surface. The discussion in the above article suggests that a variety of nanoparticles have been utilized in the drug delivery to the ocular and intraocular surface. The use of nanoparticles having the less than 10-1000nm in the drug delivery is mainly due to their ease of application and non-irritant nature. The most frequently used nanoparticles in the ocular therapy remains hydro gels undoubtedly. There are several nanoparticles which are loaded by drug molecules which carry the drugs to the ocular surface. The drugs also act on the conjunctiva and cornea of the eye. The ultimate aim of all these carriers is to increase the retention time on the surface of eye and also to improve the therapeutic effect of the drug concentration at the targeted site. In certain experiments it was proved that the mucoadhesive properties have a great influence on the drug effect on the ocular surface like the poloxamer and chitosan.When we look into the facts of largely emerged technology in the present day world there is a drastic improvement compared to the past studies and experiments. The overall views and prospects have increased to meet the needs to overcome several problems in the field of drug delivery and medicine.Chitosan nanoparticles are promising vehicles for ocular drug delivery

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