International Journal of Ophthalmology & Visual Science
2017; 2(4): 98-105
http://www.sciencepublishinggroup.com/j/ijovs
doi: 10.11648/j.ijovs.20170204.14

Review Article

Recent Trends in Chitosan Based Nanotechnology: A Reference to Ocular Drug Delivery System

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To cite this article:
Varsha Gharge, Pravin Pawar. Recent Trends in Chitosan Based Nanotechnology: A Reference to Ocular Drug Delivery System. *International Journal of Ophthalmology & Visual Science.* Vol. 2, No. 4, 2017, pp. 98-105. doi: 10.11648/j.ijovs.20170204.14

Received: March 24, 2017; **Accepted**: April 22, 2017; **Published**: September 21, 2017

Abstract: A common diseased condition includes eye infections like conductivities and corneal disorder such as glaucoma etc. Some of the typical classes of drugs used for the ocular delivery are miotics, mydriatics/cycloplegics, anti-inflammatory, anti-infective, surgical adjuvant and diagnostics. This review presents an outline of the prospective of chitosan-based nanomedicine for the treatment of ocular infection for improving the corneal residence time and *in vitro* bioavailability. In addition, its minimum toxicity and good ocular tolerance, chitosan exhibits constructive biological behavior, like bioadhesion and good permeability with optimum physiochemical characteristics, which make it a unique biocompatible material for the ophthalmic application. The review summarizes the application of chitosan based nanomedicine such as nanoparticles, solid lipid nanoparticles, nanosuspention, nanosponge and nanogels for the treatment of ocular diseases. The results reported provide evidence of the potential of chitosan being natural polymers for enhancing therapeutics effect of drugs.

Keywords: Chitosan Nanoparticles, Nanomedicine, Corneal Residence Time, *In Vitro* Bioavailability

1. Introduction

For majority of ophthalmic disorders are treated with commonly chemical agent wich includes anti-inflammatory, anti-infectives, surgical adjuvant and diagnostics. They are meant for therapy of local eye disorders. However, conventional drug delivery systems: which includes solutions, suspensions, gels ointments and inserts, suffers with the problems such as drug drainage from instilled solutions, tear turnover, poor corneal permeability naso-lactrimal drainage, systematic absorption and blurred vision and hence demand for novel approaches for ocular medicine [1]. Past few decades witnessed significant advancement of research, particularly in the development of advanced drug delivery system intended for optimized and controlled delivery of ocular therapeutics to the target sites either by increasing its penetrations across mucosa or by prolonging contact time of carrier with ocular surface [1].

The inert, biodegradable, biocompatible and lack of immunogenicity properties have conferred in natural polymers as potential carriers in drug delivery systems. The eyes are the most sensitive body organ responsible for vision. So, it is important to carefully deliver the drugs through this route. The major problem with the ocular disease treatment is to provide and maintain an adequate concentration at the site of action for a longer time interval. The solutions have been found to exhibit a very short residence time in the *cul-de-sac* due to rapid clearance, naso-lachrymal drainage or ocular irritancy.

Chitosan is a cationic polysaccharide of co-polymers glucosamine and N-acetyl glucosamine. The N-acetyl-2-amino- 2-deoxy-D-gluco-pyranose units are linked by b-D (1, 4) glycosidic linkages. It is naturally found in the fungal cell walls. Commercially, it is obtained by the alkaline deacetylation of chitin present in the crustacean shells of crimps, lobster and crab. Deacetylation of chitin renders chitosan free of cellulose-like properties due to the presence of four elements in its formula, positive charge and consequent capacity to form polyelectrolyte complexes and nitrogen derivatives, according to the chemistry of the primary amino group. It possesses the ability to form films which is absent in cellulose [1]. A deacetylation of 85% or higher than 85% is

preferred due to its stronger mucoadhesive properties and biocompatibility [2]. Increasing the molecular weight and decreasing the deacetylation degree lead to increased irritation scores in rabbits [3]. Strong mucoadhesion occurs due to strong electrostatic interactions which occur between the positively charged amino groups present in chitosan and negatively charged sialic acid residues present in mucus [4]. It is a nontoxic and biodegradable polymer. Chitosan is soluble at acidic pH (pH <5) but precipitates as the physiological pH (pH 7.4) is restored. Charges are induced in chitosan molecules in acidic and basic media which lead to their swelling but they do not swell in the neutral media [5]. The poly cationic chitosan HCl significantly increased the residence time of formulation and the drug penetration as compared to the polyanionic N-carboxymethyl chitosan and poly(vinyl alcohol) [6]. Chitosan--hydrochloride ofloxacin microparticles dispersed polyethylene oxide (PEO-900) inserts showed increased insert erosion and transcorneal penetration of ofloxacin. Significantly higher peak concentrations (greater than the MIC 90%) in the aqueous humor were obtained than PEO inserts [7]. Chitosan can disrupt the corneal tight junctions and enhance the transcorneal permeation of hydrophilic drugs like acyclovir by diffusion [8]. Trimethyl chitosan significantly increased the transcorneal transport of dexamethasone through the transcellular route, but did not affect tobramycin transport through the paracellular route [9]. Similarly the fluorescent chitosan--hyaluronic acid nanoparticles were found to have transported through the transcellular route [10]. Another report of chitosan in solid lipid nanoparticle formulation of cyclosporine has been published. A improved the lipid carrier properties and increased the permeation of drug across the rabbit corneal epithelium in the *in vitro* and through excised pig cornea in the *ex vivo* studies as compared with the cyclosporine a suspension [11]. In care of reports a lyophilized sponge like *acyclovir* ocular minitablets were prepared using chitosan 1%; these minitablets of acyclovir showed the slowest swelling rate and higher sustained release as compared to tablet contains sodium carboxymethylcellulose, HPMC, xanthan gum and Carbopol 943P [12].

The pupil size of rabbit treated with pilocarpine nanosuspension prepared using a combination of chitosan and polyacrylic acid remained decreased for more than 5 hours as compared with pilocarpine in simulated tear fluid and commercial eye drops which were effective for only 4.5 hours and 2.5 hours respectively [13]. The chitosan-loaded mycophenolate mofetil nanosuspension was 391% and 159% more bioavailable than the negatively charged suspension and nanosuspension without chitosan. The positively charged chitosan-loaded nanosuspension had a longer contact time with the negatively charged corneal surface while the negatively charged nanosuspension was quickly expelled from corneal surface due to the forces of repulsion [14].

In many scientific reports, chitosan has been reported as a suitable biodegradable polymer for preparation of nano- and microparticles for controlled drug release. In nanotechnology, chitosan based nanoparticles offers many advantages like better stability, low toxicity, simple and mild preparation methods, providing versatile routes of administration and has gained more attention as a drug delivery carrier [15]. Chitosan also have tendency to control the release of active pharmaceutical ingredients. In addition, chitosan is a linear polyamine containing a number of free amine groups that are readily available for cross linking whereas its cationic nature allows for ionic cross linking with multivalent anions [16].

2. Method of Preparation of Chitosan Nanoparticle

2.1. Emulsification-Cross Linking Method

In this type of preparation method, novel surfactant-polymer nanoparticles can be efficient encapsulation and sustained release of hydrophilic agent. As per US food and drug administration inactive ingredients data base, some of surfactant like dioctyl sodium sulfosuccinate and sodium Alg AOT is an anionic surfactant that is approval for oral, topical and intramuscular excipient.

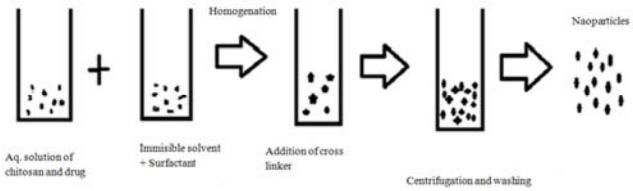

Figure 1. *Emulsification-cross linking method.*

2.2. Emulsion Solvent Evaporation Method

This method involves, the emulsification of the polymers solution into an aqueous phase followed by the evaporation of the polymers solvent which induces the precipitation of polymer nanosponges required. Mostly double emulsion solvent evaporation (w/o/w) method is used for loading biothearapeutics into polymeric nanoparticles. Firstly, an aqueous protein solution emulsified in organic phase Secondly, w/o/w emulsion is produced by adding w/o into an aqueous phase with emulsion remaining organic solvent can be removed by evaporation.

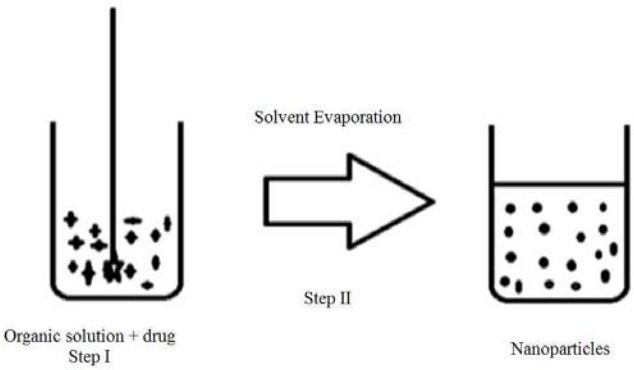

Figure 2. *Emulsion Solvent Evaporation Method.*

2.3. Co-precipitation Method

Chitosan based nanoparticles with a high degree of size uniformity were prepared by grafting techniques. In which, D, L- lactic acid on chitosan can be produced to serve as longer drug release. In one of the study, lactic acids grafted chitosan nanoparticle was prepared by co-precipitation method to form coacervate drops of aluminum hydroxide.

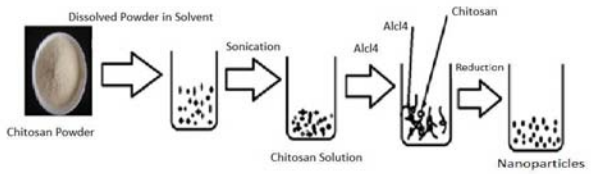

Figure 3. *Co-precipitation Method.*

2.4. Iontropic Gelation Method

The principal of this method depends upon electrostatic interaction between amine group of chitosan and negatively charged group of polyanion such as tripolyphosphate (TPP). In some research paper, the structural changes can be also introduced by ionic strength variations like presence of potassium chloride at low and moderate concentrations produced swelling and weakness of chitosan-TPP.

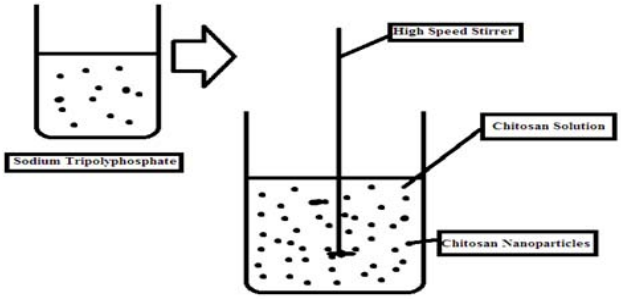

Figure 4. *Iontropic gelation method.*

2.5. Micro-emulsion Method

Formations of chitosan conjugate by using free amino group of chitosan with glutaraldehyde. This technique can be controlled particle size by varying the amount of glutaraldehyde which is responsible to change in the degree of cross-linking.

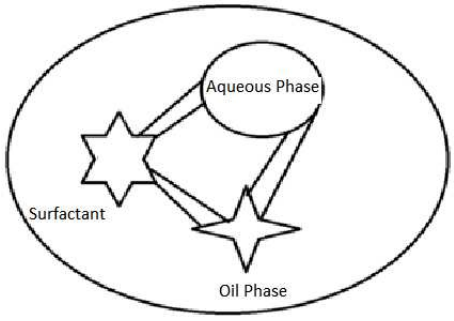

Figure 5. *Microemulsion Method.*

2.6. Complex Cocervation Method

Complex coaservation is a spontaneous phase separation process involving two liquid phase in colloidal system, which results by the interaction of two oppositely charged polyelectrolyte upon mixing in an aqueous solution. The process leads to formation of micrometric or nanomertric colloidal particles, depending on substrate or process variables, such as pH, temperature, molecular weight, ionic strength, polyelectrolyte's concentration, and so forth the major drawback of this method is poor drug stability and lower drug loading efficiency, which, however, can be overcome by cross- linking of the complex by chemical reagent, such as glutaraldehyde.

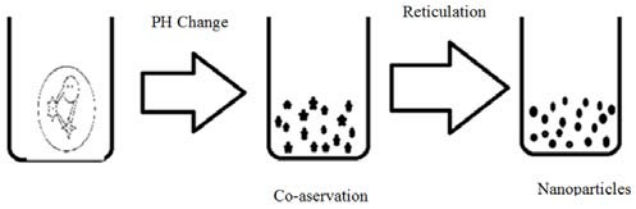

Figure 6. *Complex cocervation method.*

3. Applications of Chitosan Nanoparticles in Ocular Drug Delivery System

As antibacterial therapy for ocular infection like bacterial endothalmitis, chitosan based nanoparticles loaded with daptomycin has produced significant to prevent the growth of bacteria *in vitro* microbiological assay. The study also report the importance of chitosan on interprets and stability of nanoparticles in ocular application [17]. Some of the existence of antifungal activity of amphotricin B against *Candida albicans,* chitosan based nanoparticles showed higher concentration of amphotericin B in systemic circulation as compared with free amphotricin B formulation [18]. The scientific reports also able explore the potential of chitosan in the form mucoadhesive properties in antibacterial agent like levofloxacin loaded chitosan nanoparticle landed *in situ* gelling system which produced marked higher corneal surface result maximum bioavailability as compare to marketed formulation [19]. Similarly, the chitosan based nanoparticles of ketorolac tromethamine produced higher mucoadhesion and chitosan effect on reaction of drug on the eye surface relatively longer time. Same properties of chitosan also explored for the antiviral agent like 5- Fluorouracil (5-FU). The penetration of 5-FU through nanoparticles, chitosan enhanced mucoadhesive ness of nanoparticles and produced nano-irritant and tolerable carrier for ocular keratatis infection. The studies also focus on enhancement viscosity due to chitosan solution can able to increase the bioadhesion of nanoparticles [20].

In another study, chitosan has been reported as viscosity enhancer in sodium alginate chitosan nanoparticles of 5-FU in ophthalmic application. The report also explains about the effect of chitosan coating on mucoadhesive nature of

nanoparticles [21].

Some of the advantages also produced by derivatives of chitosan in nanocarriers system used in the treatment of glaucoma. In this study, neat chitosan and its derivatives in the nanocarriers for ocular release of timolol maleate has been reported. The chitosan derivatives were showed higher entrapment efficiency and higher diffusion carrier from drug as compare to chitosan based nano formulations [22]. Similarly, chitosan based bexaxolol hydrochloride nanoparticles core found to have promising delivery system for the treatment of glaucoma [23].

In retinal drug delivery system, chitosan precede substantial helps for biodistribution and release of cefuroxim in the specific segment of the eye in the form of nanoparticle with combination of sodium alginate [24]. In another some study chitosan – gelatin based nanoparticles of dexamethasone showed marked affinity for retina after intravitreal administration [25].

Nanogels containing loteprebnoletabonate nanoparticles by using cross linked shell technology of poly (butylene adipate)-co-N-succinyl, chitosan has been reported as an anti inflammatory carrier for ocular drug delivery system [26]. For the administration of some steroids, chitosan based nanoparticle play rational role in the penetration of hydrocortisone butyrate by producing higher emulsification capacity over the corneal epithelial surface. This study also suggest that hydrocortisone butyrate nanoparticles based thermo sensitive gel for ophthalmic formulation, chitosan emulsified nanoparticles showed significant cytotoxicity than poly (D. L. Lactic- co-glycolic acid) nanoparticles. The study also suggest that chitosan based nano system can be considered as promising drug carrier system for anterior eye disease [27].

In carteolol loaded nanoparticles chitosan amplify the hypertensive effect in betamethasone induced glaucoma in rabbit model. The pharmacological effect can be measured by using γ-scintigraphy technique in rabbit eye. The technique was able to confirm that due to presence of chitosan nanoparticles able to spread better and ocular retention time is less then as compare to aqueous solution of carteolol [28].

In another corneal penetration investigation report, cationic chitosan has been reported as penetration enhancer for cylosporina transport through nanoparticles due to charge, chitosan easily and rapidly bind with muecin surface and maximum amount drug in the control and conjunctival surface via nanoparticles [29]. In similarly study, the effect of charged chitosan has been studied and reported that due to presence of chitosan increased bioadhesion of nanoparticles and able to overcome the odd number instillation of eye drop [30]. In combination with sodium triphosphate, chitosan was able to produced a significant mucoadhesive effect and sustain the action of brimonidine tartrate in the form of nanoparticles [31]. In similar, the chitosan based brimonidine ophthalmic solutions containing nano form of drug for the treatment of glaucoma has been investigated. The result showed being nanoparticles form of single drop of brimonidine containing chitosan produce extended reduction in intraocular pressure (IOP) compare to marketed formulation [32].

In lecithin combination effect, chitosan nanoparticles have able to increase the pre-corneal higher ocular bioavailability in micelle form and aqueous form. This combination show extended intraocular pressure reduction compared then pluronic based nano particles containing melatonin in predicated model [33]. In another combination effect of both chitosan and dextran sulphate has been showed significantly high antimicrobial activity of moxifloxacin loaded nano particles in this study the chitosan was able to prove its strong mucoadhesive property in nanoparticles which helps to prolong action [34]. In one of the comparative study of different mucoadhesive molecules like hyaluronic acid, carboxy methyl cellulose, hydroxypropylmethyl cellulose and chitosanthe ability of polymer to form interaction with ocular mucin has been analyzed by using surface plasma response technique. The stability suggests that compare with mucoadhesive polymer, chitosan has been more prominent interacting molecules to form good interacting bond with ocular mucin. Thus using proper concentration of chitosan in the formulation can increase the ocular bioavailability [35]. Withpoly (lactic-co-glycolide acid) combination, chitosan showed marginal effect on the mucoadhesive properties in case of nanoparticles system [36]. In another similar combination effect also studied fluorescent rhodamine nanocomplex system [37]. The investigation also able report the transport of rhodamine was follows transcellular mechanism due to presence of chitosan in the nanocomplex revealed by after confocal microscopy study [38].

Some of other reports like combination with other synergistic agent like hyaluronic acid, chitosan produced higher mucoadhesion on ocular surface through nanoparticles. A significant reduction in intraocular pressure due to presence of chitosan in the nanocomplex system and increased efficiency of dorzol amine hydrochloride nanoparticles [39].

In gene therapy, this combination technique has been utilized and achieved the maximum bioadhesion in the hyaluronan-chitosan based DNA nanoparticles. This combination technique also able suggests that by using chitosan with hyaluronan were produced optimum zeta potential values for maximum amount penetration of gene in ocular surface [40]. Thediclofenac release from combined based nanoparticles of chitosan and hyaluronicacid was achieved more sustain than hydroxypropyl methyl cellulose based diclofenac films [41].

In different derivatives of chitosan which are employed in the nanoparticles system like trimethyl based chitosan nanoparticles has been help to penetrate higher amount of diclofenac-sodium lyophilized state. Due to presence of chitosan diclofenac sodium loaded nanoparticles showed maximum ophthalmic bioavailability as compared to marketed eye drops [42]. Similarly, a water soluble chitosan derivative i.e. 6–o-carboxymethyl have tendency to reduce the intraocular pressure when it used in nanosystem of dorzolamide. This chitosan derivative also helps to produce less eye irritation and greater bioavailability of nanoparticles [43].

A modified chitosan like thiolated chitosan based nanoparticles showed buffer mucoadhesive property and able to

penetrate the amount of drugs in to HCE cells in cornea [44]. The low molecular weight chitosan have been demonstrated in solid, lipid nanoparticles of methazolamide for the treatment of glaucoma. The low molecular weight of chitosan derivative presented a better permeation property in excised rabbit cornea and lowering intraocular pressure in sustained manner [45].

In anti-scarring study, chitosan was reported as anti-scarring agent, when it used with antiproliferative agent in after glaucoma filtration surgery. The chitosan also proved lower toxicity with high wound healing property in nanoparticles [46]. In another study, 5-fluorouracil composed nanoparticles, chitosan was reported as penetration enhancer in rabbit model. The study suggest that chitosan based nanoparticles of 5-fluorouracil was able to produced significantly higher amount of drug in aqueous humor if rabbit eye [47].

In nanostructure therapy, Econazole nitrate containing nanostructures prepared by using polyanionic cross-linker technology, chitosan produced controlled release of Econazole nitrate by strong mucoahesive ability composed than without chitosan- Econazole nitrate ophthalmic solution [48].

In self-aggregated grafting of chitosan with poly (lactic) acid copolymer produced significance mucoadhesion of amphoterian B loaded nano particles. The grafting of confirm by usingnuclear resonance and X-ray defraction technique and this grafting has been reported as prolonged mucoadhesive polymer for ocular drug delivery [49].

Chitosan in surface- modified nanostuctured lipid carriers for the improvement in transcorneal penetration has been reported a partially deacetylated water soluble chitosan based nano structured lipid formulation provide significantly higher peak concentration of flurbiprofen with minimum ocular irritation [50]. Gatifloxacin nanoparticles and minitablets prepared by using chitosan and sodium alginate gave a sustained release for 24 hours proceed by an immediate release during the first hour [51]. High cyclosporine association efficiency and loading were obtained in chitosan-coated nanoparticles. A fast release during the first hour followed by a more gradual release during a 24 hour period was obtained by in vitro study [52]. In liposome-chitosan nanoparticles complexes, chitosan loaded nanoparticles coated with lipid carriers gave more exposure to ocular surfaces and strong cellular uptake *in vivo* [53].

The role of chitosan in cationic core shell liponanoparticle was explored. The plasmid-laden chitosan nanoparticle was designed for ocular system. The study was able report on that the due to chitosan coating on nanoparticles produced superior cellular uptake and better DNA protecting effect [54].

In methicillin resistant *staphylococcus aureus* caused endophthalmitis chitosan coated alginate dapthomycin nanoparticles has reported for retinal cell monolayer penetrate agent [55].

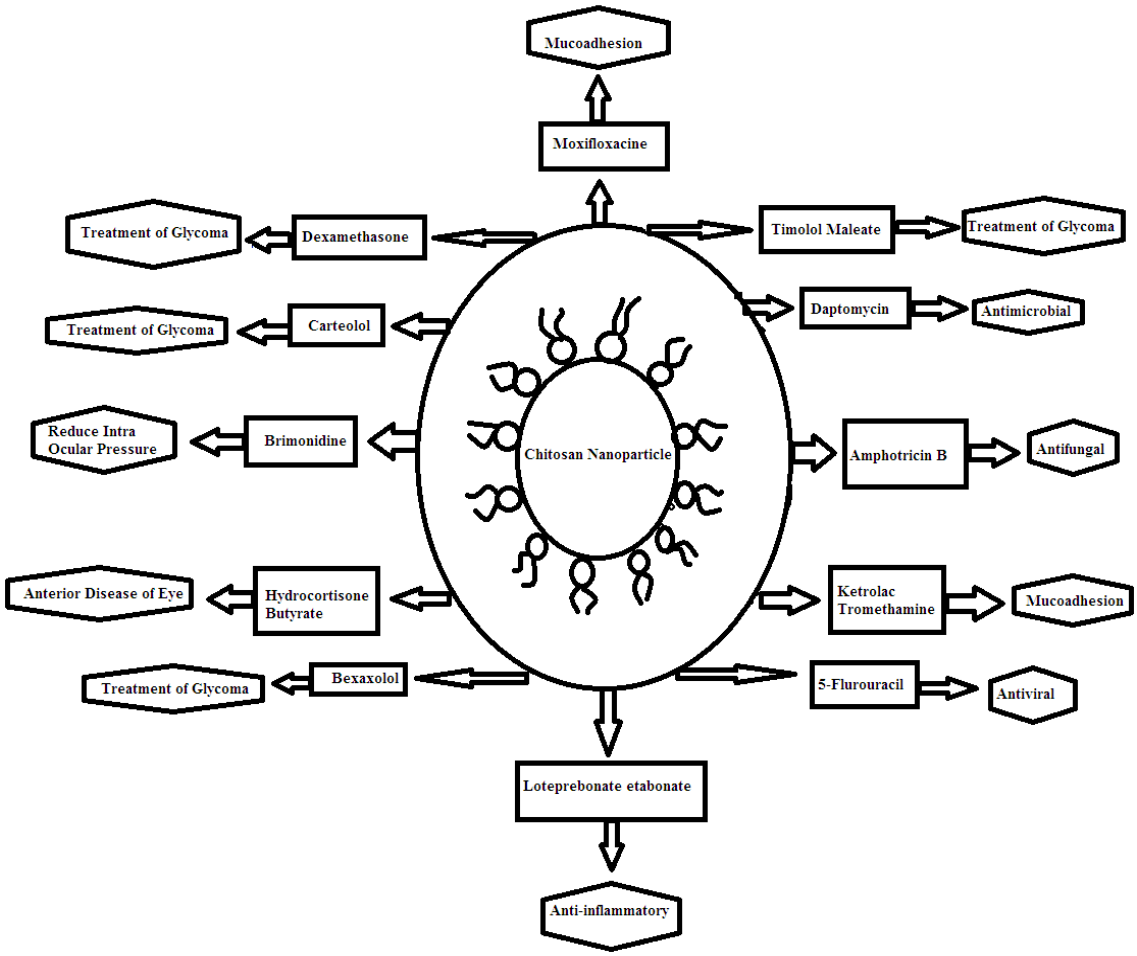

Figure 7. *Applications of chitosan nanoparticles in ocular drug delivery system.*

4. Conclusion

The conclusion of this it gives the chitosan nanoparticles for novel drug delivery for ophthalmic application by using various methods of preparation and application of it. Chitosan has been reported as a suitable biodegradable polymer and also it is natural polymers for enhancing therapeutics effect of drugs. The preparation of nanoparticles use for controlled drug release for ophthalmic application.

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