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Review On Strategies For Improving Ocular Drug Bioavailability And Corneal Wound Healing With Chitosan-Based Delivery Systems.

*Dhananjay A.Chavan, Bhaskar U. Chavan
Department of Pharmaceutics, SLSA D.Pharmacy College Mukhed, Tal Mukhed Dist Nanded Maharashtra. (431715)

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ABSTRACT:
The main inconvenience of conventional eye drops is the rapid washout of the drugs due to nasolacrimal drainage or ophthalmic barriers. The ocular drug bioavailability can be improved by either prolonging retention time in the cul-de-sac or by increasing the ocular permeability. The focus of this review is to highlight some chitosan-based drug delivery approaches that proved to have good clinical efficacy and high potential for use in ophthalmology. They are exemplified by recent studies exploring in-depth the techniques and mechanisms in order to improve ocular bioavailability of the active substances. Used alone or in combination with other compounds with synergistic action, chitosan enables ocular retention time and corneal permeability. Associated with other stimuli-responsive polymers, it enhances the mechanical strength of the gels. Chitosan and its derivatives increase drug permeability through the cornea by temporarily opening tight junctions between epithelial cells. Different types of chitosan-based colloidal systems have the potential to overcome the ocular barriers without disturbing the vision process. Chitosan also plays a key role in improving corneal wound healing by stimulating the migration of keratinocytes when it is used alone or in combination with other compounds with synergistic action.

Keywords: chitosan, chemical modification, physical gels, ocular drug delivery, corneal wound healing,

I. INTRODUCTION:

The major difficulty in treating ocular diseases is to provide and maintain an optimal ocular concentration of the drug for a long period of time [1]Eye is one of the challenging organs for drug delivery because of its unique anatomy restricts drug absorption into deeper tissues [2]. Topical instillation is by far the preferred route of administration in the treatment of anterior segment diseases. Ophthalmic drops are the most commonly-used formulations due to the ease of administration and patient compliance. However, the bioavailability of the active substance is less than 5% due to anatomical and physiological constraints such as lacrimal turnover, blinking reflex, nasolacrimal drainage or ocular barriers. Only a very small volume of lacrimal fluid (7–9 μL) is physiologically found on the eye surface, while a droplet bottle releases a higher volume of fluid [3].In eye drops only small portion of drug penetrates through corneal layer and arrives in the internal tissue present in the eye. [4]. Furthermore, the high surface tension of an aqueous drop prevents spreading on the ocular surface. Another disadvantage of the aqueous solutions is that since most of the chemical entities are lipophilic or high molecular weight compounds, their solubilization requires the addition of oils or surfactants that disturb the vision process and decrease the patient's tolerability [5].

The first structural barrier of the eye is represented by the cornea, a transparent, avascular tissue. It consists of 5 layers: 3 cellular (epithelium, stroma, endothelium) and 2 interfaces (Bowman membrane, Descemet membrane) [6]. The epithelium and endothelium of the cornea have a high lipid content, which restricts the permeability of polar, water-soluble compounds. The stroma, which is a hydrophilic layer, is made up of 70–80% water, and it represents a barrier to liposoluble compounds [7].

Melanin binding affects the pharmacokinetics of the drugs. Topically-applied substances permeate the cornea to aqueous humor, reaching melanin-containing tissues such as iris and the ciliary body. Melanin binding is associated with increased retention in the pigmented tissues, leading to a prolonged response of therapeutics [8].

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Chitosan is a polymer obtained by alkaline or enzymatic deacetylation of chitin, which is the main component in the exoskeleton of marine organisms such as crab, lobster, squid, shrimp, insect cuticle, the cell wall of some fungi and other organisms such as algae or yeasts. [10]. Chemically, chitosan consists of repeating units of N-acetyl-D-glucosamine and D-glucosamine linked by β-(1-4) glycosidic bonds (Figure 1) [11].

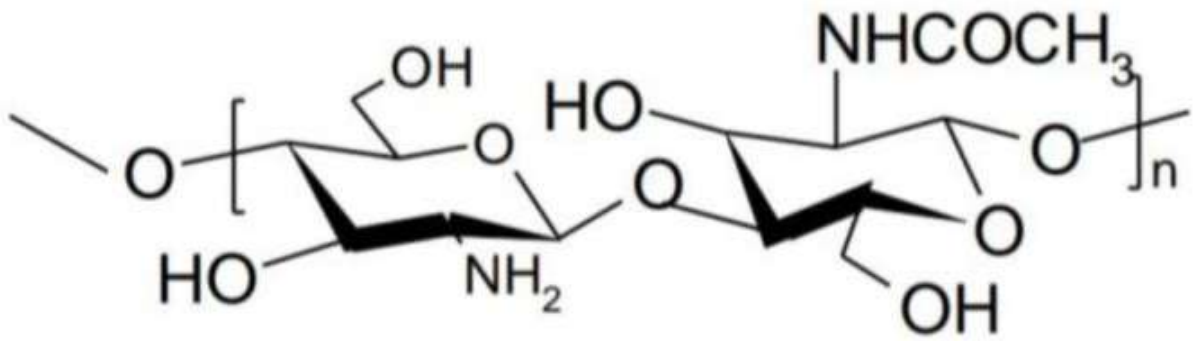

Fig: structure of chitosan

Chitin and chitosan possess interesting biological properties, so they have numerous applications especially in the medical and pharmaceutical fields. Chitin has low utilization compared to chitosan because it is insoluble in water and chemically unreactive. For this purpose, chemical modification of chitosan and chitin has been used to increase solubility and extend the spectrum of application [12]. Chitosan derivatives are obtained by chemical modification using techniques such as acylation, alkylation, hydroxylation, quaternization or esterification and have properties superior to unmodified chitosan [13].

Chitosan is a natural polymer and an inexpensive biomaterial, being an attractive excipient in the pharmaceutical industry by including it in various formulations such as prolonged or controlled drug delivery systems, wound dressings, hemostatic sponges, tissue engineering scaffolds or space filling implants [14].

Chitosan is a suitable candidate in ophthalmic formulations due to its biocompatibility, biodegradability, non-toxicity, mucoadhesive character, antibacterial and antifungal effects 15-17. Its solutions have viscoelastic and pseudoplastic properties that do not disturb the tear film. Chitosan increases the permeability of the mucosal barriers and promotes wound healing [18]. It plays a key role in improving corneal wound healing by enhancing keratinocyte migration, which leads to rapid increase in collagen synthesis [19]. Cui et al. have shown that chitosan promotes the proliferation of the corneal epithelium during healing of an injury on the rabbit eye. Corneal wound healing is mediated by the activation of the extracellular signal-regulated kinases (ERK), a subfamily of mitogen-activated protein kinase (MAPK) [20].

The main purpose in the development of ophthalmic formulations is to obtain an optimal concentration of the active substance and to maintain it for a longer period of time, thusreducing the frequency of administration [21]. To overcome the inconvenience of topical ophthalmic preparations, researchers have approached two strategies:

1. Increasing corneal residence time using viscosity enhancers, mucoadhesive agents and in situ gels;
2. Increasing corneal permeability using penetration enhancers, prodrugs and colloidal systems such as nanoparticles and liposomes [22].

In this review, we highlight some chitosan-based drug delivery systems that proved to have good clinical efficacy and high potential for use in ophthalmology. They are exemplified by recent studies exploring in-depth the techniques and mechanisms in order to improve ocular bioavailability of the active substances. Some research works are developed by exploiting the potential of chitosan in promoting corneal wound healing when used alone or in combination with other compounds with synergistic action.

II. STRATEGIES TO INCREASE RESIDENCE TIME ON THE OCULAR SURFACE:

2.1 Viscosity enhancer:

Some ocular drug delivery systems aim to achieve prolonged retention with reduced

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frequency of administration. Slightly viscous solutions are recognized as having better patient compliance. Increasing the viscosity of a preparation influences drug bioavailability by improving ocular retention time. It seems to be a tight range of viscosity between 15 and 18 centipoises (cPo), because the product must have negligible visual effects. Furthermore, it should be filterable and sterilized [23]. Tears have a viscosity of 1.5 mPa·s, but non-Newtonian flow due to the presence of mucin and other macromolecules. Studies have shown that a viscosity below 10 mPa·s leads to undetectable changes in drainage rate and does not affect ocular retention time [24].

Natural and synthetic polymers have been shown to be useful in ophthalmic formulations due to viscosity-increasing properties [25]. These polymers added to ophthalmic solutions result in a slow elimination rate from the ocular area. Often, cellulose derivatives (methylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose), poly(vinyl alcohol) (PVA) and poly(vinylpyrrolidone) (PVP) [26] are used. The addition of such polymers into ophthalmic formulations requires adequate technological solutions, as they may cause blurred vision due to changes in corneal refraction index or difficulty in instillation of a precise dose [25].

Hydrogels made up of chitosan alone show poor mechanical strength, low elasticity due to intrinsic rigidity of the chains and lack an efficient control of drug delivery. The addition of other polymers leads to the formation of polyelectrolyte complexes (PEC) with increased mechanical properties while maintaining all the properties of chitosan. PECs are preferable to chemical hydrogels, as there is no need for the addition of catalysts [27]. Hydrogels can be formed by polymer mixtures of chitosan with other non-ionic polymers such as poly(vinyl alcohol) (PVA) [28]. The combination of the two polymers is based on characteristics such as biocompatibility, biodegradability, non-toxicity and water solubility [29]. The gelling process of PVA determines the formation of a porous network in which junction points are represented by crystallites. Structural organization is described by a relative arrangement of chains in fringed micelle-like crystals and interactions between neighboring chains. Studies have confirmed that cross-linking of the gel occurs under the action of crystallites [30]. In the case of chitosan-PVA mixtures, increasing chitosan concentration negatively affects the formation of PVA crystallites by forming hydrogels with less ordered structures [28]. A studyassessed the in vitro release of in situ gels based on Poloxamer 407 and chitosan. The addition of PVA (0.2%–0.3%) significantly prolonged ocular retention. According to the authors, the release rate of the system containing PVA was higher compared to that of the PVA-free system. The formulation exhibited a pseudoplasticbehavior at 35 °C. The authors suggested that the association consisting of 20% poloxamer, 0.2% chitosan and 0.3% PVA (w/w) is a suitable formulation for ocular delivery of ciprofloxacin [31]. The development of chitosan-based biomaterials has potential for many applications due to its minimal foreign body sensation and intrinsic antibacterial properties. The field of tissue engineering allows the development of artificial cornea that adheres to the native cornea. Thus, it is necessary to create a scaffold with mechanical and transparent properties similar to the natural cornea. Seyed and Vijayaraghavan prepared and analyzed the properties of a PVA/chitosan-based scaffold cross-linked with 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) and 2 N-hydroxysuccinimide (NHS) for in vitro delivery of cultured corneal epithelial cells. The viscosity of the solutions was measured using the Brookfield viscometer. For a 90:10 chitosan/PVA mixture, the viscosity value was 1726 cPo. A linear increase in viscosity for PVA solutions was also observed after the addition of increasing amounts of chitosan. Thus, blending chitosan with PVA solutions has the effect of thickening and increasing viscosity. The amino and hydroxyl groups of chitosan form hydrogen bonds with the PVA groups, leading to the formation of uniform nanofibers even at low PVA concentrations [32].

Cellulose derivatives are used in liquid formulations as viscosity enhancers. They are pH-sensitive polymers and have active surface properties that influence blinking rate [33]. Ahmed et al. incorporated polylactide-co-glycolide (PLGA) nanoparticles into polymeric gels in order to release ketoconazole. Hydroxypropyl methylcellulose (HPMC) was added to all preparations as a viscosity enhancer. The results showed that the addition of HPMC to chitosan-based formulations increased the viscosity following contact with simulated lacrimal fluid [34]. Silva et al. incorporated nanoparticles of chitosan, sodium tripolyphosphate and hyaluronic acid into a polymeric HPMC solution for ocular delivery of ceftazidime. The HPMC gel entrapped ceftazidime molecules, leading to prolonged release of the active substance. The diffusion rate of ceftazidime from nanoparticles could be modulated

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by varying vehicle viscosity. The drug diffusion through HPMC gel was lower than that of the nanoparticles alone because the enhanced gel viscosity produced a more compact polymeric matrix that decreased the diffusion rate of the active substance. HPMC does not have ionized groups to interact with the sialic acid residues of mucin. Therefore, HPMC's ability to increase the drug retention time in the eye is more related to its capacity to enhance viscosity rather than to any interactions with mucus [35].

Due to the viscosity-enhancing effect, chitosan solutions enable the ocular retention of nanoparticles [36]. Chitosan-coated sodium alginate-chitosan nanoparticles with 5-fluorouracil (5-FU) were prepared by the ionic gelation technique and then suspended in chitosan solution, which is responsible for the enhanced viscosity, as nanoparticles did not show any interaction with mucin. In vivo study on rabbit eye showed a higher level of 5-FU in aqueous humor compared to 5-FU solution (Figure 2). The alginate shell was obtained by cross-linking with chitosan, which took place spontaneously through electrostatic interactions between negatively-charged carboxyl groups of alginate and protonated amino groups of chitosan [37].

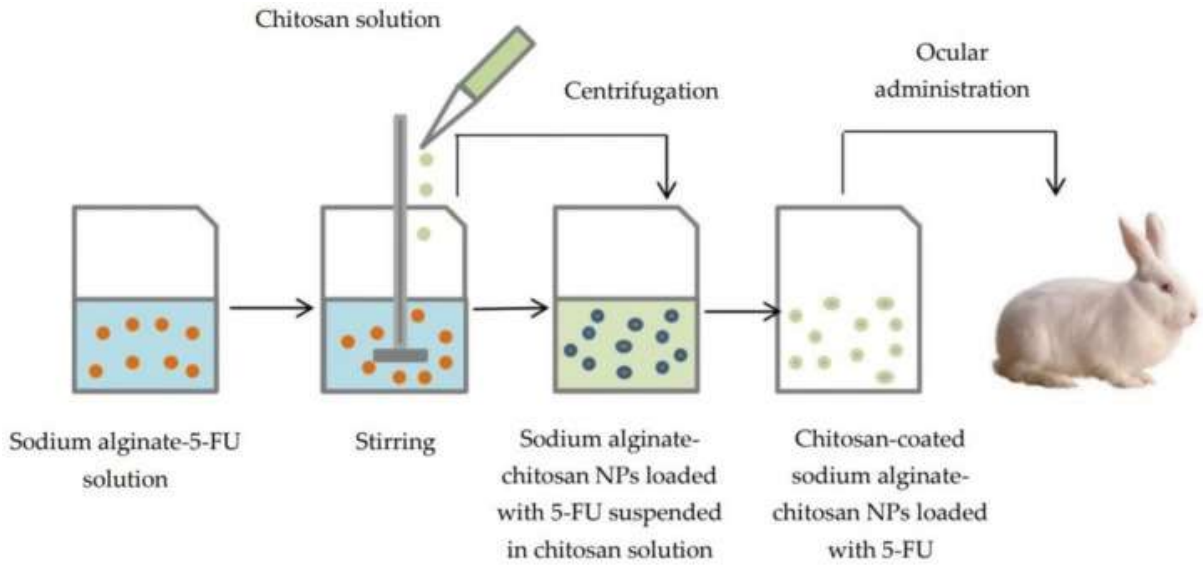

Fig2: Preparation of chitosan-coated sodium alginate-chitosan nanoparticles with 5-flurouracil (5-FU)

2.2 Mucoadhesiveagents:

Mucoadhesive delivery systems have the advantage of adhering to the mucous membrane layer. Mucosal adhesion increases the retention time of drugs and protects small, vulnerable molecules. The overall effects result in a controlled release of drugs with improved bioavailability and better patient compliance [38].

The mucinous layer keeps the film on the eye surface and creates an unfavorable environment for the growth of pathogens. Other important roles are to maintain the ocular surface moisturized, an optimal refractive index at the air-water-cornea interface and to keep solubilized proteins in tears [39]. Mucin is negatively charged at physiological pH (7.4) due to sialic acid residues from the terminal ends of the mucopolysaccharide chain, resulting in a preferential intake for cationic molecules. The use of positively-charged formulations is the most common way to increase the bioavailability of ocular formulations [7]. Chitosan has an attractive potential in improving the permeability through the mucosal epithelium due to its cationic structure and mucoadhesive character [40]. At low pH, the amino groups are protonated, and the polymeric macromolecules become positively charged. The cationic structure determines electrostatic interactions with the negatively-charged groups of sialic acid from epithelial surfaces (Figure 3). The mucoadhesive character is also influenced by hydrogen bonds and hydrophobic interactions [6].

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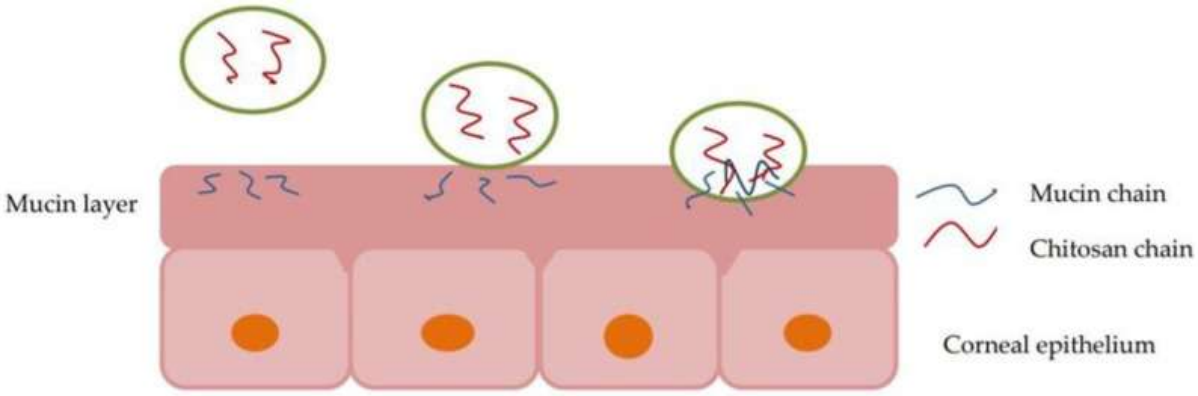

Fig3: Interactions between chitosan chains and the mucin layer.

The mucoadhesive mechanism implies two different phases: the contact phase and the consolidation phase. The first one involves the intimate contact between the mucoadhesive agent and the mucus, leading to the spreading and swelling of the formulation. In the consolidation phase, the mucoadhesive agent is activated by the presence of moisture, which allows the molecules to break free and to link up by van der Waals forces and hydrogen bonds. According to diffusion theory, mucoadhesive molecules interact with glycoproteins from mucus, forming secondary bonds [40].

In a study initiated by Yamaguchi et al., the effects of chitosan coating of an ophthalmic emulsion with indomethacin were analyzed. The authors evaluated the degree of retention of the chitosan-coated emulsion in lacrimal fluid and compared the results with those of an uncoated emulsion. The study showed a prolonged retention time of indomethacin in lacrimal fluid for the coated emulsion. The detachment force of coated chitosan emulsion from mucin was considerably higher than that generated by an HPMC emulsion with a similar viscosity, as a result of the mucoadhesive character of chitosan. According to researchers, the chitosan-coated emulsion proved to be a promising formulation for enhancing the bioavailability of indomethacin due to its adhesion to the ocular surface [41].

2.3 Ocular In Situ Gels:

In-situ gelling systems is defined as that it is the polymeric solutions which forms the viscoelastic gel by undergoing sol-gel phase transition in response to environmental stimuli or by having change in environment of the dosage form.[54]. These formulations also combine the advantages of solutions such as accuracy and reproducibility of dosing, ease of administration, minimum interference with vision (absence of blurred vision, lack of sticking eyelids) with prolonged corneal residence, resistance to nasolacrimal drainage, reduced frequency of administration and characteristics of ointments [55]. These ophthalmic forms containing polymers are liquid at room temperature (25 °C) and undergo sol-gel transition upon contact with the ocular surface [56]. Depending on the physiological mechanisms that produce the gelation of polymers, there are three major categories of polymers:

1. Temperature-triggered in situ gelling polymers. The phase transition temperature is called the low critical system temperature (LCST). Below this value, the hydrogen bonds between the hydrophilic groups of the polymer and the water molecules improve dissolution of the polymer, and the system is a solution. As the temperature rises, the hydrogen bonds break, hydrophobic interactions appear and sol-gel transition takes place [57].
2. pH-triggered in situ gelling polymers. pH-responsive polymers contain weak acidic or basic groups that release or accept protons in response to pH changes. Thus, conformational changes occur in the polymer structure that determine its swelling.
3. Ion-triggered in situ gelling polymers. Cross-linking of sensitive polymers takes place due to monovalent or divalent cations in the tear film [58].

III. STRATEGIES TO INCREASE CORNEAL PERMEABILITY:

3.1 Permeation enhancer:

Increasing drug permeability through corneal epithelium can be achieved by using permeation enhancers that transiently decrease corneal barrier resistance. The addition of

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penetration enhancers to an ophthalmic solution reduces the size of the instilled drop and improves the bioavailability of poorly absorbable substances. Most substances are surfactants that alter the physical properties of cell membranes by removal of phospholipids or membrane solubilization. Benzalkonium chloride is a conventional permeation enhancer that alters the ocular barrier, but can lead to toxic effects by accumulation in the cornea for several days. The mechanism of action of ethylenediaminetetraacetic (EDTA) is to alter tight junctions between superficial epithelial cells and to facilitate paracellular transport [59].

Numerous studies have demonstrated the potential of chitosan as a permeation enhancer for the absorption of hydrophilic drugs. Chitosan is able to adhere to the surface of the mucosa and temporarily open tight junctions between cells. Majumdar et al. evaluated the effect of chitosan, benzalkonium chloride (BAK) and disodium ethylenediaminetetraacetic acid (EDTA), alone and in combination, on acyclovir permeability through the rabbit excised cornea. The authors observed that 0.1% chitosan alone increased acyclovir permeability by 3.1 times, while chitosan at the same concentration in the presence of the other two promoters generated a 5.5-fold increase. The conclusion of the study was that the association of the three compounds resulted in a significant increase in corneal permeability of acyclovir and that chitosan improved the diffusion of hydrophilic compounds through the corneal membrane [60].

3.2 Prodrug:

Prodrugs are pharmacologically inactive compounds and derivatives of molecules that require chemical or enzymatic transformation for the release of the active substance. Enzymatic transformation of prodrugs into ophthalmic tissues is used to release the parent drug. Active substances possess hydroxyl or carboxyl groups, which can be esterified to produce lipophilic compounds. The activity of esterase is 2.5-fold higher in the corneal epithelium compared to stroma and endothelium. Absence of acetylcholinesterase and butylcholinesterase in tears allows the absorption of the prodrug through the corneal epithelium. Incorporation of prodrugs into various delivery systems associates an enhanced permeability of the active substance through the cornea with prolonged precorneal retention (61).

Ganciclovir is an antiviral compound that has significant activity on human cytomegalovirus. The partition coefficient is low, so that the ocular bioavailability is poor . Thus, Kapanigowda et al. incorporated ganciclovir into chitosan microspheres. Polymeric microspheres had the advantages of easy administration in liquid form and rapid diffusion in ocular tissues. The polymeric matrix of chitosan facilitated diffusion of the microspheres. A positive zeta potential enabled adhesion to the surface of the cornea and prevented nasolacrimal drainage. Microspheres interacted with the cell membrane, resulting in a structural reorganization of proteins of tight junctions. Thus, transcorneal permeability was achieved. The concentration of ganciclovir in the aqueous humor of Wistar rats afteradministration of the microspheres was significantly higher than that obtained from the instillation of a solution.

3.3 Colloidal systems: Nanoparticles and Liposomes

Colloidal systems are likely to provide a controlled drug release with prolonged pharmacologicaleffects. Such an objective can be achieved by a retention localized in the cul-de-sac where the entrapped drug can be delivered by diffusion or under external stimuli such as light. These formulations may have prolonged contact with the ocular surface, withstanding ocular clearance mechanisms. To achieve the optimal effect, it is necessary to create mucoadhesivenanosystems in order to enhance ocular bioavailability [62]. Different types of chitosan-based nanosystems have an increased ability to improve ocular drug delivery. Hydrophilic and hydrophobic drugs, as well as biomacromolecules can be delivered after inclusion in chitosan-based colloidal systems. Depending on whether chitosan is in the form of a coating or a nanomatrix, nanocarriers can be chitosan-coated or chitosan-based nanosystems. Nanoparticles have a diameter of less than 1 μm and are made up of natural or synthetic polymers in which the drug is dissolved, incorporated or encapsulated. Drugs can also be integrated into the matrix or surface. Nanoparticles are well tolerated by patients . Nanoparticles have been designed to overcome ocular barriers, increase drug permeability and maintain optimal concentration of active substances in target tissues.

IV. CONCLUSION:

Overcoming the inconvenience of conventional eye drops is a difficult task because the eye is a sensitive organ and the formulations must be safe and efficient without disturbing the vision process. In order to increase drug

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bioavailability, two strategies have been developed that involve increasing ocular contact time and enhancing corneal permeability. Chitosan is a versatile polymer used in ophthalmology due to properties such as biocompatibility, biodegradability, mucoadhesive character and antimicrobial activity. Chitosan plays a key role in improving corneal wound healing by stimulating the migration of keratinocytes, which leads to rapid growth of collagen production. Used alone or in combination with other compounds with synergistic action, chitosan increases ocular retention time and corneal permeability. The presence of the amino group and the cationic behaviour in acidic solutions explain the unique properties among other biopolymers. Chitosan-based drug delivery systems such as in situ gels, nanoparticles or liposomes provide ease of administration, protection for entrapped drugs, rapid release, increased ocular retention time and bioavailability of the active substances.

Nowadays, most chitosan-based systems are designed for the ocular delivery of a single therapeutic agent, so in the future, they could be improved by associating active substances with synergistic action to enhance the therapeutic effect in the treatment of ocular disorders.

The eye is a sensitive organ, and the viscosity of a gel can create discomfort for certain patients. Rigorous viscosity control in the formulation process is necessary to avoid such inconvenience. Nanoparticles can cause blockage of punctal drainage, so further studies are necessary to assess the risks of prolonged and repeated administration of these pharmaceutical forms.

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