WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 12, 395-406. Review Article ISSN 2277–7105

A COMPREHENSIVE REVIEW ON NANOPARTICLE BASED TOPICAL OPHTHALMIC FORMULATIONS

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Article Received on
01 Aug. 2021,

Revised on 22 Aug. 2021,
Accepted on 11 Sept. 2021

DOI: 10.20959/wjpr202112-21682

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ABSTRACT

Ocular diseases in the anterior and posterior segment diseases. Because of complicated structure of anatomy and physiology of the eye, efficient ocular drug delivery is a great challenge to researchers and pharmacologists. Although there are conventional non-invasive and invasive treatments, such as eye drops, injections and implants, the current treatments either suffer from low bioavailability or severe adverse ocular effects. Newer emerging nanoscience and nanotechnology are important in the development of novel strategies for ocular disease therapy. Several active molecules have been designed as nanocarriers to overcome ocular barriers which is responsible for only 1-5% of drug to reach the ocular tissues. Nanocarrier drug delivery system will interact with specific ocular tissues. In this review, we elaborated on the recent attempts of nanotechnology-based systems for imaging and treating ocular diseases, such as corneal diseases, glaucoma, retina diseases, and choroid diseases. Although additional work remains, the progress described herein may pave the way to new, highly effective and important ocular nanomedicines. The review includes in situ ophthalmic gelling systems and ophthalmic solution which the prominent delivery systems. This review emphasis on improvement ophthalmic drug bioavailability, there are considerable efforts directed towards newer drug delivery systems for ophthalmic administration.

KEYWORDS: Nanoparticles, Gels, Hydrogels, In situ gel, Polymers, Gelling mechanism.

INTRODUCTION

Ocular diseases directly affect human vision and quality of life. According to survey 285 million people suffer visual impairment Of these, 65% are over 50 years old, and 82% of blind patients are over 50.[1]

However, due to the special physiological barriers and anatomical structures of the human eye, diagnoses and treatments of these disorders can suffer from low efficiency and lack of specificity. The current therapeutic methods seldom can completely restore vision loss or detect severe ocular diseases at an early stage.[2] Therefore, the development of improved diagnostics and therapeutics for ocular diseases is receiving intense attention.

Ocular drugs are mostly applied locally to the surface of the eye as eye drops for treatment of either the external ocular infections such as conjunctivitis, blepharitis, keratitis sicca, or intraocular diseases such as glaucoma, proliferative vitreoretinopathy, endophthalmitis, recurrent uveitis, acute retinal necrosis and cytomegalovirus retinitis etc.[1] Due to efficient protective mechanisms of the eye (e.g. lachrymal secretion, blinking reflex) and systemic absorption in the conjunctiva, major part of the drug is rapidly eliminated from the ocular surface and only a small fraction of drug is absorbed into the eye, which results in poor bioavailability of the drugs. This needs frequent dosing of eye drops, which causes pulse kinetics of the drugs in the eye.[2]

Newer Emerging nanotechnology and nanoscience methods are increasingly being applied to biopharmaceutics. Nanoscience is an interdisciplinary field that combines material science, physics, chemistry and biology, whereas nanotechnology involves the design and fabrication of different materials in nanometer scale at least in one dimension.[3, 4, 5, 6] Several nanotechnology-based strategies have been developed and aimed at management of ocular diseases: bioadhesive enhancement, sustainable release, stealth function, specifically targeted delivery, and stimuli responsive release, etc.[7, 8, 9] Therefore, many attempts have been focused on fabrication of multi-functional nanosystems for ocular diseases therapy by improving drug (or gene) delivery to both the anterior and posterior segments of the eye.

In this review, we have focused on advances in development of nanotechnology-based systems for ocular diseases therapy and imaging. First, the specific anatomy and the attendant constraints in ocular drug administration are introduced. Some conventional and alternative drug administration routes are summarized and compared as well. Second, for a deeper

insight of nanosystems mechanism, several examples of nanosystems for management of ocular disease are highlighted and reviewed. Then, some typical studies are summarized. Finally, we summarize the perspective of nanotechnology and existing challenges in ocular diseases therapy and diagnosis. This review will provide both inspiration and impetus for better design and development of intractable ocular disease managements.

2. Ocular anatomy and constraints to ocular drug delivery

The human eye is a globular structure organ with size of about 24 mm, and consists of two main parts: the anterior and posterior segments (Fig. 1). The both parts have various biological barriers to protect the eye from foreign substances. The anterior portion includes the corneal, iris, lens, and aqueous humour. The posterior portion consists of the vitreous body, retina, choroid, and back of the sclera. The cornea is transparent and contains five layers: epithelium, Bowman′s membrane, stroma, Descemet′s membrane, and endothelium.[11, 12] The human corneal epithelium is the most important part of corneal barrier since it has multilayers of corneal epithelial cells which interconnect by tight junctions. These tight junctions can severely limit ocular penetration of drugs, especially many types of hydrophilic molecules. The corneal stroma is mostly composed of charged and highly organized hydrophilic collagen which hinders passage of hydrophobic molecules.[13, 14, 15] In recent studies, various efflux transporters on epithelial cells were proved to be of importance in preventing permeation of anti-viral and anti-glaucoma drugs.[16, 17, 18]

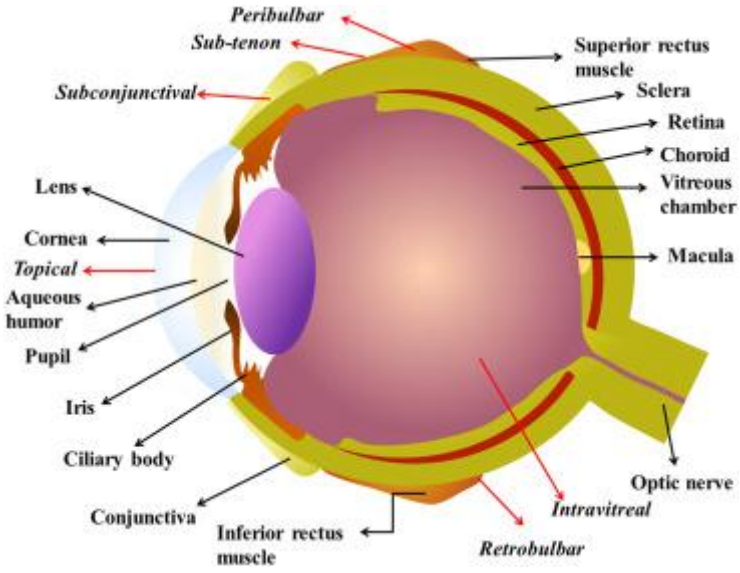

Fig. 1: The anterior and posterior segments.[10]

Advantages and limitations of ocular delivery routes

Ocular dosage forms include viscous solutions, suspensions, ointments, hydrogels etc. Viscous solutions are beneficial over eye drops but may have the risk of obstruction of the puncta and canaliculi. Suspensions based ocular drug delivery formulations are generally used for administering poorly soluble drugs, but the grittiness and irritation on application due to suspended particles limits their application and also it suffers high variability in efficiency 5. The variability in efficiency in case of ocularly applied suspensions may be due to the non-uniformity of the doses. Ointments are not used greatly because of the risk of uneven volume administration, greasiness and blurred vision.[4,5,6] The drawbacks like inaccurate and irreproducible drug administration, crusting of eyelids, and lachrymation associated with the preformed hydrogels, limiting their application as ocular drug delivery systems. Clearly the existing ocular delivery systems are primitive and inefficient to treat severe ocular diseases, thus cannot be used extensively for ocular drug delivery.

In ocular therapy, a liquid dosage form is preferred from the point of patient acceptability. Thus, an ideal ocular drug delivery system is the one, which can be administered in drop form without causing any problem in normal vision, can produce sustained drug release and does not require frequent dosing. The main advantage of such a system is the opportunity of accurate and reproducible administration of drugs in reproducible manner, and increased drug bioavailability by prolonged retention 1.

In situ gelling systems can fulfil these criteria successfully as they can be retained at the ocular surface for longer duration and thus can increase the residence time of the drug at the site of action, resulting in enhanced drug bioavailability and lesser patient incompliance as compared to conventional ocular drug delivery system.[10] A wide variety of drug molecules and materials of therapeutic advantages such as antibiotics (Ofloxacin, Ciprofloxacin, Gatifloxacin), beta blockers (Timolol, Carteolol), NSAIDs (Ketorolac Tromethamine, Indomethacin), Pilocarpine hydrochloride, Pueraria, Antivirals (Acyclovir) has been delivered through *in situ* gelling systems, which shows the importance of *in situ* gelling formulations as the future drug delivery systems.[7-9,11-25]

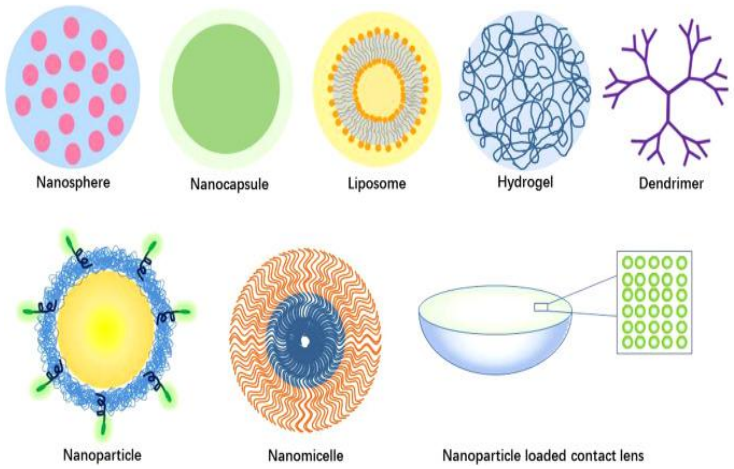

Fig 2: Newer techniques in situ ophthalmic drug delivery.[10]

Importance of in situ gelling system and Nanotechnology in ocular drug delivery[7, 8]

It helps for the controlled and sustained release of the drug by its special 'Sol Gel transition.' It helps for the reduced frequency of drug administration of the drug in the body. Low dose of the drug is required and there will be no drug accumulation and no side effects. The bioavailability of the drug will be more. There will be increased residence time of the drug due to gel formation. The in-situ gel system decreases wastage of the drug, Liquid dosage form that can sustain drug release & remain in contact with cornea of eye for extended period of time is ideal. Reduced systemic absorption of drug drained through the nasolacrimal duct may result in some undesirable side effects. Nano-particles have proven to have low toxicity as well as long term stability. It is able to be mass produced and therefore it shows promise in terms of therapy. Nano-particles are mainly advantageous as compared to the ocular therapeutic counterpart due to its capacity for large bioavailability of drugs. When compared to the previous amount of bioavailability that was available with traditional ocular therapy, the nano-particle alternative is extremely favourable. Another advantage that nano-particles have is the ability to pass though barriers that conventional drugs cannot.

METHODS OF PREPARATION OF NEWER TECHNIQUES – 1. OPHTHALMIC IN SITU HYDROGEL

Photo-polymerization

In photo-polymerization method electromagnetic radiations are used during formation of in situ gelling system. A solution of reactive macromere or monomers and invader can be injected into a tissues site and the application of electromagnetic radiation used to form gel. The most suitable polymers for photo polymerization are the polymers which undergo dissociation by polymerisable functional group in the presence of photo initiator like acrylate

or similar monomers and macromers that are typically long wavelength ultraviolet and visible wavelengths are used. Short wavelength ultraviolet are not used often because they are limited penetration of tissue and biologically harmful. In this method, ketone, such as 2,2 dimethoxy-2-phenyl acetophenone, is used as the initiator for ultraviolet photo-polymerization. camphor quinone and ethyl eosin initiators are used in visible light systems. Various approaches of in situ gelation Various approaches are made in order to get in situ gelation system.

Temperature triggered in situ gel: Temperature is the most widely used stimulus in environmentally responsive polymer systems in in-situ gelling formulation. The change of temperature used in easy to control, and also easily applicable both in vitro and in vivo. In this system, gelation is caused due to body temperature and no need of external heat. These hydrogels are liquid at room temperature (20–25°C) and undergo gelation when in contact with body fluids (35– 37°C), due to an increase in temperature. There are three types of temperature induced systems. They are negatively thermo sensitive type Eg: Poly (Nisopropylacrylamide) positively thermo sensitive type Eg: polyacrylic acid thermally reversible type Eg: poloxamer, Pluronic's, Tetronics. In this system, thermo responsive or temperature responsive polymers are used that show a drastic and discontinuous change in their physical properties with temperature. These polymers show a miscibility gap at high or low temperature an upper or lower critical solution temperature exists.

pH triggered in situ gelation: In this system gel is formed due to pH changes. In this method pH sensitive polymers or pH responsive are used. In pH sensitive polymers includes pendant acidic or basic groups that may accept or release protons in counter to changes in environmental pH. The large number polymers of ionizable groups are known as poly electrolytes. The poly electrolytes are present in the formulation causes increase in external pH that leads to swelling of hydrogel that forms in situ gel. Some suitable polymers for this approach those polymers having anionic groups. Some are cellulose acetate phthalate (CAP), carbomer and its derivatives, polyethylene glycol (PEG), pseudo latexes and poly methacrylic acid (PMC) etc.

Ion activated in situ gelation: In this method, gelling of the solution instilled is triggered by change in the ionic strength.[23,24] It is assumed that the rate of gelation depend on the osmotic gradient across the surface of the gel. The polymer which shows osmotically induced gelation is Gelrite or Gellan gum, Hyaluronic acid and Alginates etc.

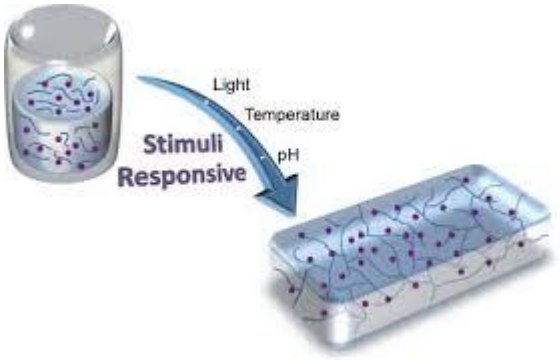

Figure 1: Mechanism of In situ gel formation.

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METHODS OF PREPARATION OF NEWER TECHNIQUES – 2. NANOPARTICLES CARRIER MEDIATED OPHTHALMIC DRUG DELIVERY

SOLVENT DISPLACEMENT METHOD

It is also called as nanoprecipitation method and has been widely used to prepare nanoparticles. The method is based on the precipitation of preformed polymer following displacement of a semi polar solvent miscible with water in the presence or absence of surfactant. The basic principle of this technique is similar to spontaneous emulsification of the organic phase containing drug and polymer into the external aqueous phase. In this method the polymer and drug are dissolved in a water miscible organic solvent of intermediate polarity (e.g., acetone and ethanol). The resulting organic phase is injected into a stirred aqueous phase containing a surfactant as stabilizer. The nanoparticles are formed instantaneously during the rapid diffusion of the organic phase into the aqueous phase.40

HOMOGENIZATION

This method is also used for preparation of nanosuspension. The process can be summarized into three steps: firstly, the presuspension is formed by dispersing the drug powders in a stabilizer solution; then pre-suspension formed was then homogenized by the high-pressure homogenizer at a low pressure for several times. It is also called as premilling, and finally the pre-milled suspension was homogenized at a high pressure for 10-25 cycles until the nanosuspensions with desired particle size were prepared.61

IONIC GELATION

In the ionic gelation method, the positive or negative charge of the hydrophilic polymer is complexed with a multivalent cationic (e.g., calcium chloride) or polyanionic (e.g., sodium tripolyphosphate) to form highly viscous gel particles with a size in the range of a nanometer. Ionic gelation method was developed by Calvo and Co-workers for the preparation of chitosan nanoparticles. In this method polymer solutions and polyanion solutions are mixed to form nanoparticles. The basic mechanism involved in the formation of nanoparticles is the electrostatic interactions between positively charged amino groups present in polymer and negatively charged anion. In other words, it can be seen that in the ionic gelation method, due to interaction the material undergoes transition from liquid to gel phase. The obtained chitosan nanoparticles generally are of small size in the range of 200-500nm.[24]

MILLING METHOD

High-shear media mills or pearl mills are used to prepare nanosuspensions. The media mill consists of three parts- a milling chamber, a milling shaft and a recirculation chamber. As a result of impaction of the milling media with the drug, high energy and shear forces are generated which provide the necessary energy to disintegrate the microparticulates drug into nanosized particles. The balls or milling media are ceramic-sintered aluminium oxide or zirconium oxide or highly cross-linked polystyrene resin and have high abrasion resistance. The size below 0.1 μm is achieved by planetary ball mills. In the media milling process, the milling chamber is charged with the milling media, water or suitable buffer, drug and stabilizer. Then milling media or pearls are rotated at a very high shear rate.[26]

SOME RESEARCH WORKS DONE ON DRUGS

Following are the some of the works carried out on some of the drugs used to treat ophthalmic diseases based on *in situ* gel forming drug delivery.

Moxifloxacin hydrochloride

Moxifloxacin hydrochloride is the drug mainly used in the treatment of some infections occurred in the eye like conjunctivitis etc. It is formulated as the in-situ gel forming formulation by using sodium alginate and HPMC as polymers.[24]

Sesbania grandiflora

It is an extract of flower which is also mainly used to treat some bacterial infections noticed in the eye. Here, the polymers used are pluronic F127 and chitosan where phase transformation takes place due to change in temperature.[25]

Dexamethasone and ciprofloxacin hydrochloride

The use of ciprofloxacin is it acts as an antibiotic which is used to treat bacterial infections of the eye and dexamethasone is a potent anti-inflammatory drug used to treat inflammation caused during infection. To formulate this combination of drugs is gellan gum.[16]

Olopatadine hydrochloride

Oloptadine HCl is the drug mainly used in the treatment of allergic reactions it is a class of anti-histaminic drug to formulate this drug as In-situ forming gel the polymers used are Carbopol and HPMC E-50LV acts as a PH triggered system.

Norfloxacin

Norfloxacin is the drug which is mainly used to treat bacterial infections like conjunctivitis. The polymers used to formulate this drug are carbopol-940 and HPMC-E50LV and the formation of gel takes place due to pH change.

Ketorolac

Ketorolac is anon-steroidal anti-inflammatory drug. Here the polymers used are carbopol 940 and HPMC. Here also gel formation takes place due to the changes in Ph.[17]

Dorzolamide Hydrochloride

This drug is mainly used in the treatment of glaucoma. The polymers used for formulating this drug are sodium alginate and Hydroxy propyl cellulose. The main mechanism involved in the formation of the gel is due to the presence of calcium ions in the lachrymal fluid.[32]

Ciprofloxacin

Ciprofloxacin is mainly used for the treatment of eye infections like dacrocystitis, ulceration in cornea, conjunctivitis etc. The polymers used for formulating this drug are poly acrylic acid and HPMC.[18]

Voriconazole

This drug is mainly used fungal keratitis which causes vision loss. It is a broad-spectrum antifungal drug. the polymers used to formulate this drug are sodium alginate and HPMC K15M.[30]

Pilocarpine

It is the drug which is used in the treatment of glaucoma. And the polymers used are sodium alginate which mainly consists of glucuronic acid residues which are helpful for the formation of gel in the presence of calcium ions.[31]

Commercial formulation of ophthalmic drug based on *in situ* gel formation:

Timoptic-XE

This formulation is supplied from Merck and Co. Inc., which is sterile and buffered product and is isotonic with the eye. The drug present in this is Timolol maleate. It is mainly used to decrease the increased intra ocular pressure. Each ml of this solution contains 3.4mg of the drug. The other ingredients present in this are tromethamine, gellan gum, mannitol and water.[32]

CONCLUSION

Ocular drug delivery systems provide local as well as systemic delivery of the drugs. The newer and advanced ophthalmic drug delivery systems offer more protective and effective means of the therapy for the nearly inaccessible diseases or syndromes of eyes. Nanotechnology and In situ hydrogel opens new vista for agents having poor bioavailability and instability that are related with the delivery of hydrophobic drugs, including those that are poorly soluble in aqueous as well as organic media. In this review we provide the details of the method used for the preparation of nanoparticulate drug delivery along with in situ hydrogel. Including Special properties and benefits of this nanotechnology and in situ hydrogel can be considered as a new beginning in formulation technologies in the imminent years.

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