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(REVIEW ARTICLE)

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Nepafenac loaded ophthalmic nanocarriers for treatment of uveitis: A review

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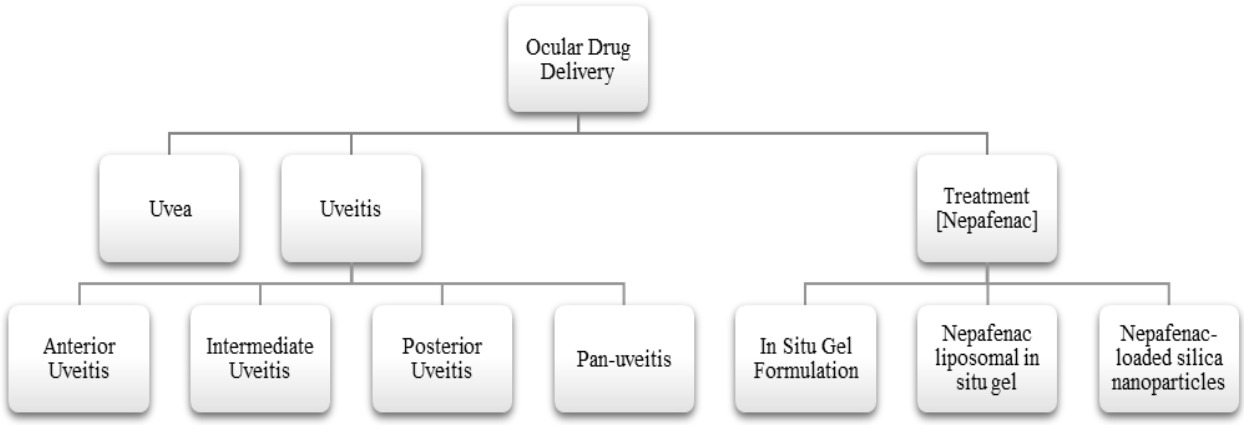
Abstract

Visual impairment (VI), a worldwide worry that is probably going to raise with delayed futures, has gained increasing attention in the domain of eye care. Now a days, new cases of visual impairment occur in older individuals, some children are born with visual impairments resulting from retinopathy of prematurity, a condition associated with premature birth. Other children experience vision loss because of congenital glaucoma or congenital cataracts, Uveitis and some experience vision loss of unknown etiology. Uveitis is an intraocular inflammation involving primarily the uveal tract. Vision is one of our most cherished senses. There are nearly 45 million people worldwide who are blind and a further 135 million people are visually disabled. Uveitis causes 0.6% - 11% of blindness in various studies. The ophthalmic preparations are available as buffered, sterile and isotonic solution. For the ocular delivery of drugs, several types of dosage forms are prepared and marketed. As drops are easier to administer so the most prescribed dosage form is the eye drop solution. Nepafenac is unique among ophthalmic NSAIDs in that it is a prodrug deaminated to amfenac, a highly effective non-selective cyclooxygenase inhibitor. The compiled data presented in this review will act as a good information resource and reference point for further research in the field of ocular drug delivery aiming non-invasive sustained release of drugs in the anterior and posterior segments of the eye.

Keywords: Ocular drug delivery; Uveitis; Nepafenac; Nanomicelles

Graphical Abstract



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1. Introduction

The field of ocular drug delivery is one of the fascinating and testing attempts confronting the drug researcher [1]. The eye is a small, sensitive, and complex organ that is separated from the rest of the body by multiple layers of biological barriers [2]. The human eye is a complex organ and measures about 24 mm in a fully grown adult. The structure of the eye is divided into 2 segments, the anterior segment, and the posterior segment. The anterior segment covers the one/third portion of the eye which mainly consists of cornea, conjunctiva, aqueous humor, iris, ciliary body, and lens. The remaining two/third portion of the eye is known as the posterior segment or back portion of the eye. The posterior segment mainly consists of Vitreous humor, retina, choroid, and optic nerve [3], [4]. In addition, the internal ocular structures and tissues are protected from the outer climatic environment by the tight intersections of the corneal epithelium and the mucosal surface [2]. Both parts of the eye (anterior and posterior) are affected by vision-threatening diseases. A few diseases affecting the anterior parts as, glaucoma, allergic conjunctivitis, anterior uveitis, and cataract. Posterior parts of the eye affect some vision-threatening diseases such as Age-related Macular Degeneration (AMD) and diabetic retinopathy macular edema [DME], proliferative vitreoretinopathy [PVR], posterior uveitis, and cytomegalovirus [CMV] [3].

The ophthalmic use of medications is the essential course of organization for the treatment of different eye infections, like Uveitis, Inflammation-Mediated Retinal Edema, etc. [5]. The conventional route of drug administration through the eye in the form of solutions, suspension, and ointment. It is estimated that 90% of marketed ophthalmic formulations are conventional dosage forms which include 62.4% solutions, 17.4% ointments, and 8.7% suspensions [6].

1.1. Uvea

The uvea is a vascular, fibrous layer that secures the eye and is basic to nourishment and gas exchange. It comprises three sections: the iris, ciliary body, and choroid. At the point when any part of the uvea gets inflamed, it is called Uveitis.

2. Uveitis

Uveitis is a sight-compromising inside the eye that influences both the uveal tract (which is made out of the iris, choroid, and ciliary body and which is the blood-providing layer within the eye) [7]. Uveitis is the fifth most normal reason for extreme visual loss and up to 20% of legal visual deficiency is because of difficulties of uveitis [8]. The most widely recognized type is an irritation of the iris called iritis (Anterior Uveitis) which generally affects the anterior segment or anterior cavity, which includes the anterior chamber, iris, ciliary body, cornea, lens, and related surrounding tissue of the eye. In uveitis, the primary focus of inflammation in the vitreous, while in posterior uveitis, the retina or choroids are affected adversely [9].

Uveitis can be categorized as infectious and non-infectious uveitis [8]. It is a treatable condition; however, without proper treatment, it can prompt different complications including glaucoma, waterfalls, optic nerve harm, retinal separation, and serious vision loss. The word Uvea originated from the Latin word ‘uva’, which means grape. Inflammation of the uveal tract is called uveitis [10].

2.1. Types of Uveitis

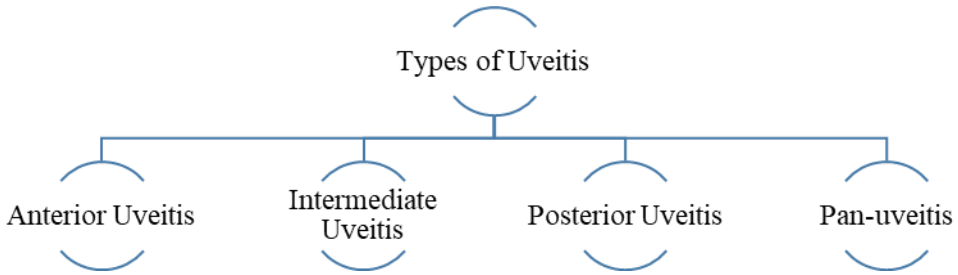

Figure 1 Different types of uveitis

2.1.1. Anterior uveitis (front of the eye)

The most widely recognized type of uveitis, it influences the iris and its surrounding tissue, the ciliary body the two of which are situated toward the front of the eye. Anterior uveitis is referred to as iritis because the iris is the part of the uvea that is normally inflamed.

2.1.2. Intermediate uveitis (middle of the eye)

Another type of uveitis, it influences the region simply behind the ciliary body (pars plana) and the most forward edge of the retina. This is the most un-basic kind of uveitis.

2.1.3. Posterior uveitis (back of the eye)

An uncommon type of disorder that influences the back part of the eye, the choroid, and can influence the retina or potentially optic nerve. This structure is harder to treat and is frequently connected with progressive loss of vision.

2.1.4. Pan-uveitis (all parts of the eye)

When irritation affects all three areas of the uvea it is referred to as pan-uveitis. Intermediate, posterior, and pan-uveitis are severe conditions and may cause visual impairment whenever left untreated. On the off chance that you experience any of the side effects underneath, contact your eye care proficiently quickly [11], [12].

2.2. Symptoms of uveitis

Uveitis comes on quickly with redness and pain or may start with slight pain and redness, but gradually obscures the vision. Symptoms of uveitis can include.

- Light sensitivity
- Blurring of view
- Pain in the eye
- Eye redness
- Floaters in the eye
- Decreased vision

2.3. Treatment of uveitis

In the course of the most recent two decades, the treatment of an assortment of ophthalmic inflammatory conditions with topical non-steroidal anti-inflammatory drugs (NSAIDs) has been getting acceptance. NSAIDs products are weakly acidic and ionize in the basic lachrymal fluid, which reduces corneal penetration.

Furthermore, In the US various new ophthalmic NSAID products have been recently introduced for commercial use, despite the novel chemical entity Nepafenac [13]. NSAIDs are prescribed to treat various pains, inflammatory conditions of the eye, osteoarthritis, and rheumatoid arthritis [1]. For cataract surgery five topical NSAIDS preparation are available in the US market i.e. bromfenac ophthalmic solution 0.09%; 0.1% diclofenac solution; 0.03% flurbiprofen solution; 0.4%, 0.45%, and 0.5% solutions of ketorolac; and 0.1% suspension of nepafenac [14]. The reported information recommends that topically administered 0.1% nepafenac might be more compelling than different NSAIDs in the treatment of posterior segment inflammation [15].

3. Nepafenac

Nepafenac is yellow crystalline or powdery substances practically insoluble in water. An aqueous suspension at 0.1%gives an average pH of 6.75. The coefficient partition n-octanolwater is 128. This substance melts at approximately 185ºC and it does not show polymorphism. Nepafenac is an achiral substance and there are no possible variations in stereochemical configuration.

In August 2005, Food and Drug Administration approved Nepafenac ophthalmic suspension 0.1% (Nevanac*). Another medication of 0.3% nepafenac ophthalmic suspension was confirmed by the FDA in October 2012. The detailing of the 0.3% quality has been changed to alter the additives and improve the pharmacokinetics of the active ingredients to allow once day by day versus the 3 times every day dosing required with the 0.1% product [16]. Chemically nepafenac is a (2- amino-3-benzoyl benzene acetamide) is a potent non-steroidal anti-inflammatory drug used to treat inflammation and pain associated with cataract surgery. In the market, there is currently available commercial formulation as a 0.1% ophthalmic suspension [13], [17]. It primarily acts on COX-1 and COX-2 [17]. Only a small amount of nepafenac suspension is administered to penetrate the cornea to reach the efficient intraocular tissue due to dilution and corneal barriers caused by lacrimation [18]. The several side effects was reported of nepafenac like, increased

intraocular pressure, reduced visual accuracy, and sticky sensation in the eye. Poloxamers are nonionic triblock copolymers that are made up of two hydrophilic polyethylene oxide (PEO) which are separated by hydrophobic polypropylene oxide (PPO). It manifested a wide range of applications in the pharmacy profession and product formulations as it acts as an emulsifier, solubilizer, polymeric surfactant, gelling agent and dispersing agent, etc. The micelles form a low concentration there, forming a clear flexible. Thermo gel at a high concentration. It has been observed that high solubility by the formation of hydrogen bond between PEO cores of poloxamer to the drug [19].

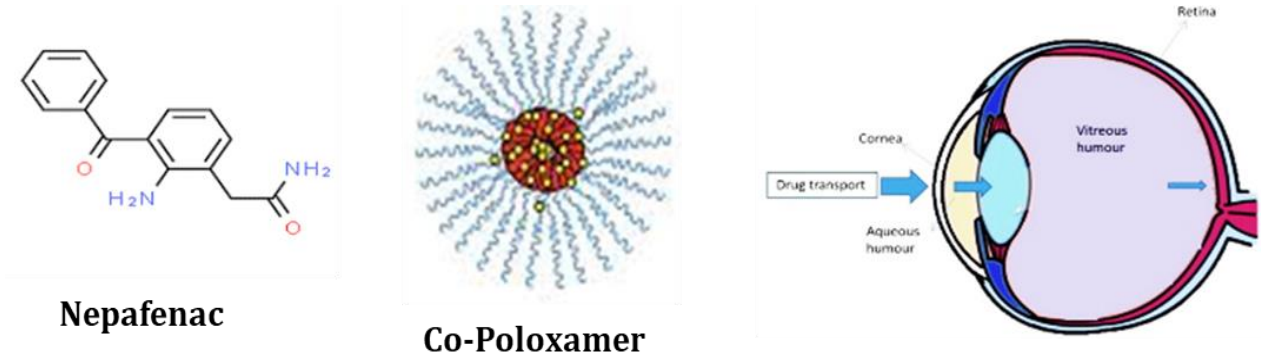

Figure 2 Incorporation of Nepafenac into Eye

3.1. Mechanism of Action of Nepafenac

Nepafenac is an NSAID pro-drug, a characteristic that may offer several benefits over other ophthalmic NSAIDs. Nepafenac has excellent corneal permeability as compared to conventional NSAIDs [15]. It permeates corneal barriers without delay as a neutral molecule and thus has an advantage over classical acidic NSAIDs [20].

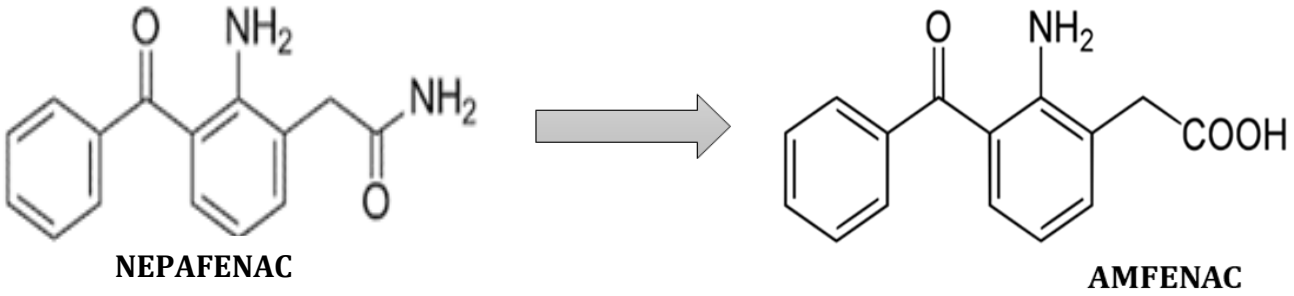

Figure 3 Nepafenac is converted to a potent cyclooxygenase inhibitor, Amfenac,

By intraocular hydrolases [21].

Amfenac is a potent anti-inflammatory yet maintains a safe therapeutic profile [15]. The conversion of nepafenac to amfenac happens dominantly in the intraocular vascular tissues, particularly in the retina and choroid. The nepafenac conversion rates are higher in more posterior sites within the eye because of the higher hydrolase activity in these tissues. It is twice as high in the ciliary body when compared with that in the cornea and multiple times higher in the retina and choroid than in the cornea.

While nepafenac exhibits some COX inhibition, the activated form, amfenac, is a potent inhibitor of both COX-1 and COX-2 activities. The analgesic action of NSAIDs has also been credited both to the reduction of PG synthesis and to an immediate impact on the sensitivity ocular nociceptor nerve terminals by nepafenac. The rapid onset of nepafenac analgesic action is probably due to natural analgesis activity and a rapid saturation of the corneal epithelial layer, highly innervated by nociceptors [51]. In the safety profile of nepafenac thinning of the cornea, slow wound healing and ulcer formation may occur. Patients having rheumatoid arthritis, penetrating keratoplasty, and person with surgically damaged corneal nerves should not use the nepafenac formulation [22]. Nepafenac is not recommended in patients with severe dry eye showing corneal staining [23].

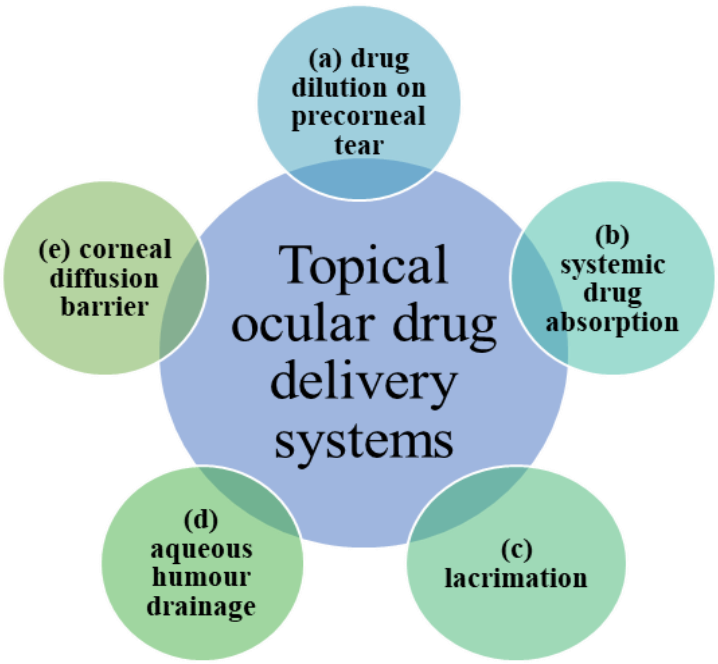

Figure 4 Types of Biological Barriers for ODDS

4. Nanocarriers for Ocular Drug Delivery

Ocular diseases directly affect human vision and quality of life [24]. There are five types of biological barriers of the eye in topical ocular drug delivery systems. Due to these barriers very low concentration of the drug reaches the target site [25]. Despite intense research efforts by pharmaceutical scientists' drug delivery to the eye in an effective manner remains a challenge. Both anterior and posterior segments provide unique barriers to the entry of drugs [26], [27]. Much of the research is directed toward the development of delivery systems with high patient compliance and ocular bioavailability [28]. Different endeavors have been made to improve the bioavailability of drug release and retaining rate from formulations or dosage forms. Designed nanodevices and nanostructures work human organic frameworks at the single-cell and molecular levels [29]. Nanotechnology and micro technology involve making and utilizing the materials, devices, or systems on the nanometer and micrometer scale respectively. These technologies are expected to play a critical role in many biomedical applications like drug delivery, molecular imaging, biomarkers, and biosensors [30].

The ophthalmic application of drugs is the primary route of administration for the treatment of different eye illnesses, and is very much acknowledged by patients; usually, only a small amount of the drug administered penetrate the cornea to reach the desired intraocular tissue because of corneal obstructions and weakening brought caused by lacrimation [18],[31]. Nanocarriers such as microemulsions, nanosuspensions, liposomes, dendrimers, liposomes, cubosomes, nanoparticles, polymeric micelles, and solid lipid nanoparticles are tested for ocular delivery to overcome the typical problems of topical therapy, such as low corneal penetration and poor drug availability [32]. These systems are easily administered as eye drops for topical delivery or injections for intraocular delivery [33]. The nanocarriers most widely used in treating anterior segment diseases will be highlighted in the subsequent section.

4.1. Limitations of ocular drug delivery

Ocular delivery of drugs suffers from the following limitations:

- Termination of the dosage form is not possible during an emergency.
- Interference with vision.
- Faces difficulty in placement and removal of the dosage form.

During sleep or while rubbing eyes, there may be an occasional loss of the drug [52].

4.2. Nanomicelles

Nanomicelles are colloidal structured carrier systems that range from 5 to 200 nm in size [34]. Micelles could be spherical or cylindrical or star-shaped depending on the molecular weight of the core and crown forming blocks [35]. Nanomicelles are suitable and safe alternatives for ocular drug delivery because of their ability to solubilize less water-soluble drugs in the hydrophobic core and form a clear aqueous formulation which is otherwise difficult to achieve for a hydrophobic drug. Nanomicelles offer a bunch of benefits like the capacity to define hydrophobic drugs into a clear aqueous solution, high water solubility, monodispersity, form structure nanosize development, ability to minimize drug degradation, reduced toxicity, enhanced permeation through tissues, and higher bioavailability [36].

4.2.1. Types of nanomicelles

- **Surfactant nano micelles**

Amphiphilic molecules ordinarily have a hydrophilic head and a hydrophobic tail. The hydrophilic head group carries an anionic or cationic charge (ionic surfactant) or both positive and negative charges (zwitterion surfactant) or no charge (nonionic surfactant) [37], [38]. The surfactant that is utilized at lower concentrations is likely to be absorbed in the surface, subsequently, it assists with lower down the surface free energy. According to the literature, the surfactant micelles are utilized to improve penetration of the topically applied drug through the cornea and enhanced ocular bioavailability.

- **Polymeric nano micelles**

Polymeric micelles are synthesized from block copolymers. They form amphiphilic monomeric units which have distinct hydrophilic and hydrophobic monomeric units. Generally, the hydrophobic core is surrounded by the hydrophilic shell. They contain polymer chains that are self-assembled due to hydrophobic or ion pair interaction between polymer segments [34]. It is found that polymeric micelles are more stable than nano micelles made from conventional surfactants.

- **Polyion complex nanomicelles**

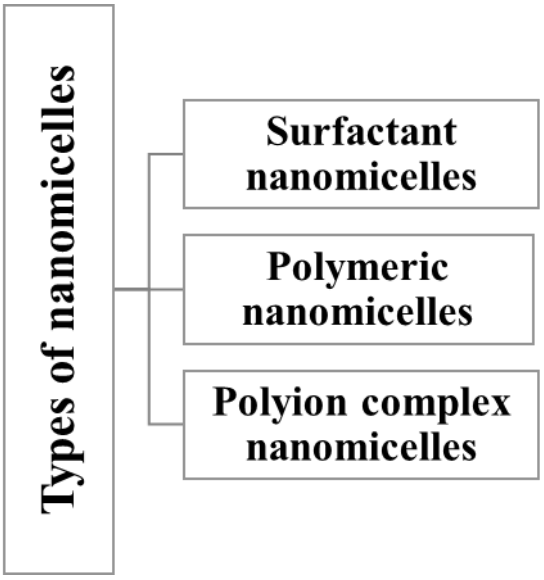

Figure 5 Types of nanomicelles

These nanomicelles are shaped by electrostatic interactions between polyion copolymers and oppositely charged ionic drugs [39]. Polyion complex is mainly utilized for gene and antisense oligonucleotide delivery [40]. For ocular drug delivery, PEG stabilizes the hydrophobic polyion drug complex by forming the polyion complex micelles. These micelles reduced side effects as it is target-specific and subsequently is a promising carrier system for ocular delivery of ionic macromolecules [19].

4.3. Methodology

4.3.1. Solvent dispersion method

In this method, volatile organic solvents are utilized to dissolve both copolymers and drugs. This method can be utilized just when both copolymers and drugs dissolved in a common solvent and where they don't dissolve in water. The organic solvent is removed by evaporation and thus the thin film of copolymer and drug are formed. Water is added to the above film to obtain drug-loaded micelles [41].

4.3.2. Direct dissolution method

In direct dissolution, the copolymer and drug are dissolved in an aqueous solvent. The hydrophobic drug preferentially is loaded into the hydrophobic core of the resulting micelles. Commonly utilized hydrophobic copolymers like poloxamers. In some cases, heat should be added to initiate micellization. The temperature is increased to form micelles through dehydration of the core-forming segment. The copolymer and the drug are dissolved in an aqueous solvent, then both solutions are mixed thus micelles are formed [42].

4.3.3. Dialysis method

The dialysis method (DM) is the most adaptable and well-known. In this method, physical separation of the dosage forms is achieved by the usage of a dialysis membrane which allows for ease of sampling at periodic intervals. Drugs in the copolymer are mixed in an organic solvent the above solution is poured into a dialysis bag is placed into a beaker containing water. This solution and the water move in and out. Dialysis method is commonly utilized that are having poor solubility. The dialysis process is taken more than 36 hours for appropriate drug loading [43], [42].

4.4. Marketed preparation for Ocular drug delivery

4.4.1. In Situ Gel Formulation

In situ gel formulation is available in liquid form which can be easy to apply on the site of absorption thus, considered as favorable in the patients, and also gives sustained drug release in the form of strong gel [44], [45]. Water-soluble polymers are mostly used because they are having the ability to shaping gels when applied to the targeted delivery site. The nature of the polymer and its concentration and different delivery systems are produced to improve the residence time of the drug in the eye [45], [46]. In situ gel system enhances the retention of nepafenac on the corneal surface. As compared to Nevanac®, all in situ gel systems show higher retention and permeation in the cornea. Also, an ion-activated in situ gel system, using Protanol PH 1033, shows the sustained release of nepafenac into the cornea [47].

4.4.2. Nepafenac liposomal in situ gel

Nepafenac-loaded liposomes have been prepared by the Rotary Flash Evaporation technique in different ratios using cholesterol and soya lecithin [48]. Optimized liposomes have been used to develop in situ gelling system. The thermoreversible nepafenac liposomal in situ gels have been prepared by using mucoadhesive polymers like HPMC E15 and chitosan and poloxamer 407 (Pluronic 127). The release of nepafenac is slowly from gels, for a period of 12 hours. Poloxamer 407/chitosan combinations have the best pH and gelation temperature which is good for drug delivery systems. Hence this combination can be used as an In situ gelling vehicle, to enhance ocular bioavailability and to improve patient compliance [49].

4.4.3. Nepafenac-loaded silica nanoparticles

Recently silica nanoparticles (SiNPs) are reported to be the suitable carriers for the ocular delivery of a drug. Because of the amorphous nature, SiNPs have stable compound structures, simplicity of surface modification, and tolerable biodegradability. The optimized SiNPs have promptly penetrated the cornea and release the drug without any harm [50].

Nepafenac-loaded SiNPs dispersed in the in-situ gel have been effectively formulated in a combination of two polymers one by using poloxamer (Pluronic F127) – poloxamer (Pluronic F68) and another one by using poloxamer (Pluronic F127) – chitosan for extending the duration of nepafenac given via topical delivery. The blank SiNPs have been prepared by Stober's process. The prepared SiNPs are spherical in shape with a smooth external surface indicated a good encapsulation efficiency and loading capacity of the drug. In comparison with poloxamer-based in situ gelling systems and Poloxamer– chitosan-based in situ gelling systems; Poloxamer– chitosan-based in situ gelling systems shows high permeation with sustained release of nepafenac. Consequently, the formulated nepafenac-loaded SiNPs dispersed in in-situ gelling systems can be the best decision for the topical therapy to the ocular disease [19].

5. Conclusion

The extensive work in ocular drug delivery during the earlier period. It has been intended, to extend the residence time of topically applied drugs in the uveal tract and conjunctiva section. Nepafenac has been proven effective against uveitis. The ocular tolerance, bioavailability, and biocompatibility of nepafenac nanoparticles have been illustrated, indicating promising outcomes regarding their physicochemical and biopharmaceutical properties. These approaches have been found to be capable of increasing the corneal contact time and improving ocular bioavailability also. Therefore, it could be concluded that modern technology seems to be logically explored in various ways over the conventional approaches, examples of non-conventional approaches being the use of nanotechnology, nanocarriers, microspheres, liposomes, appropriate prodrug *in situ* forming gel and iontophoresis as effective means of ocular drug delivery enhancing ocular absorption along with reduction in side effects.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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