International Journal of Engineering Inventions
e-ISSN: 2278-7461, p-ISSN: 2319-6491
Volume 12, Issue 4 [April. 2023] PP: 99-104

Hyaluronic Acid Based Ocular Drug Delivery System for Fungal Keratitis

AKSHAYA.P, SANGAVI.G, LAKSHIMIPRIYA.V.P, PAVITHAR.N

ABSTRACT
Hyaluronic acid (HA) is commonly used polymer in ocular drug delivery, due to its good biocompatibility, adhesion and rheological properties, which can be coupled with drugs and used as a substrate and surface modified drug carrier for drug delivery. In recent years Nano-carriers have attracted importance in the field of topical ocular drug delivery due to resolved the many issues like residence time of corneal surface, interaction with ocular surface, stability, permeability and bioavailability of drug substance.. The development of innovative, patient-compliant medication formulations and drug delivery techniques, which may overcome these obstacles and sustain drug levels in tissues, has increased over the past two decades in the field of ocular drug delivery research. An inflammation of the cornea's layers is known as keratitis. Fungi continue to be one of the most elusive and difficult to diagnose and treat among the organisms that cause keratitis. It is common for the cornea to become infected with fungi or other bacteria after being traumatized, This condition is known as fungal keratitis (FK).In this review we have clearly discussed that different type of nano-carrier system with Hyaluronic acid based ocular drug delivery system for fungal keratitis on to fabricate with different excipient having an altered dosage form properties like structure, composition, surface charge of nano-carrier are the important features for corneal interaction and transport system. The collected data evidently showed that nanocarrier system with Hyaluronic acid based ocular drug delivery system is a safe and potential carrier for the treatment of fungal keratitis.

KEYWORDS
Hyaluronic Acid, Nano-carriers, ocular Drug Delivery, Fungal Keratitis, Cornea.

Date of Submission: 01-04-2023 Date of acceptance: 12-04-2023

I. INTRODUCTION

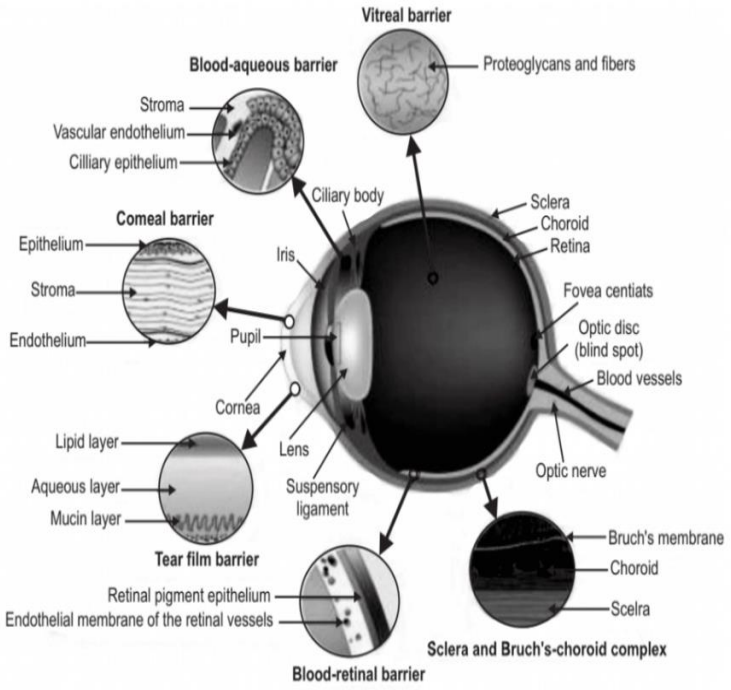
Ocular medication delivery is the main issue facing pharmacologists and formulation scientists today. The most practical and patient-friendly drug delivery method, particularly for the treatment of disorders of the anterior segment, is topical eye drops.[(1)] The development of innovative, secure, and patient-compliant medication formulations and drug delivery devices/techniques, which may overcome these obstacles and sustain drug levels in tissues, has increased over the past two decades in the field of ocular drug delivery research.[(2)] Ocular drugs are usually delivered locally to the eye. Required drug loading, release rate, and ocular retention time of drug delivery systems depend on the potency, bioavailability, and clearance target place of the medication.[(3)]. To calculate steady-state drug concentrations in the ocular compartments while accounting for drug dosage, bioavailability, and clearance, the design aid for ocular drug delivery systems is described here. Drug delivery systems for topical, intravitreal, and subconjunctival administration can be designed with the aid of the dosage rate adjustment to achieve the desired drug concentrations.[(4)] An inflammation of the cornea's layers is known as keratitis. It is frequently linked to bacterial or viral germs that enter the corneal stroma and cause inflammation before eventually destroying these structures. Fungi continue to be one of the most elusive and difficult to diagnose and treat among the organisms that cause keratitis. Additionally, it has been demonstrated that fungal keratitis (FK) infections might be more dangerous and pathogenic than bacterial infections.[(5)] Monocular blindness and other eye impairments are most commonly caused by a fungus called keratitis, which infects the cornea. It primarily affects marginalized groups more frequently. The etiology of the fungal infection that threatens the cornea is still not well understood. It is common for the cornea to become infected with fungi or other bacteria after being damaged or traumatized, such as during agricultural labour in developing nations. This condition is known as fungal keratitis.[(6)] For FK treatment, a timely carried out and accurate diagnosis method of the issue is essential. Overall, there are not many incidences of infection under temperate climate circumstances, but under tropical climate conditions, it can reach over 40% of infectious ulcers. The results of FK are less favourable than those of bacterial keratitis. In 50–70% of instances, prompt medical attention is required, and in 30–54% of cases, a corneal graft is necessary.[(7)]]. Additionally, several investigations have shown that the etiology of keratitis is significantly influenced by the patient's immune system. Nowadays, confocal microscopy, polymerase chain reaction (PCR), and optical coherence tomography (OCT) of the anterior region are employed

for the most accurate diagnosis of the FK. For instance, the danger of further effects from invasive ocular tissue sampling exists. Additionally, as the incubation period varies depending on the material and can range anywhere from 1-2 weeks to months, identifying the infection may take a while.Yeasts and hyphomycetes (Aspergillus, Fusarium) are the main dangers of infection (Candida albicans and C. parasitosis). Colletotrichum parasitosis, a pathogen that caused FK in China, has also been linked to documented cases.[8]

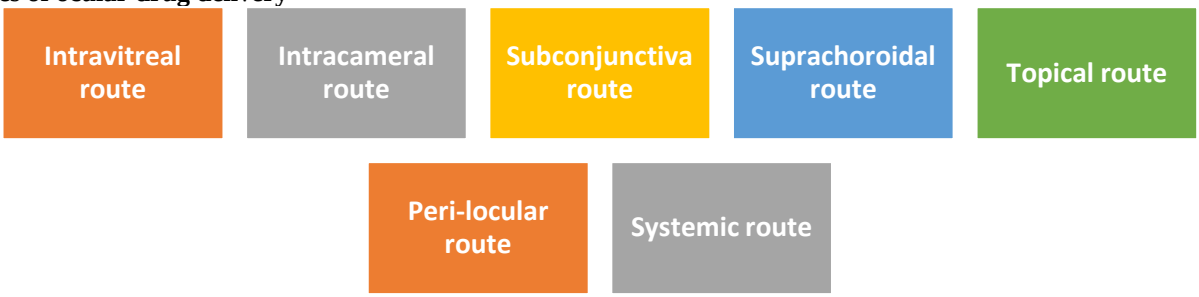
CONVENTIONAL OCULAR DRUG DELIVERY SYSTEMS

A popular and patient-friendly drug delivery method is topical drop instillation into the lower precorneal region. Only 20% (or about 7 L) of the instilled dose is kept in the precorneal pocket after being applied topically, as most of it is lost to reflux blinking . The drug's concentration in the precorneal region serves as a catalyst for its passive diffusion through the cornea. However, greater corneal penetration with longer drug cornea contact time are necessary for effective ocular drug administration with eye drops.[9]

Barriers for ocular drug delivery



Routes of ocular drug delivery



FUNGAL KERATITIS

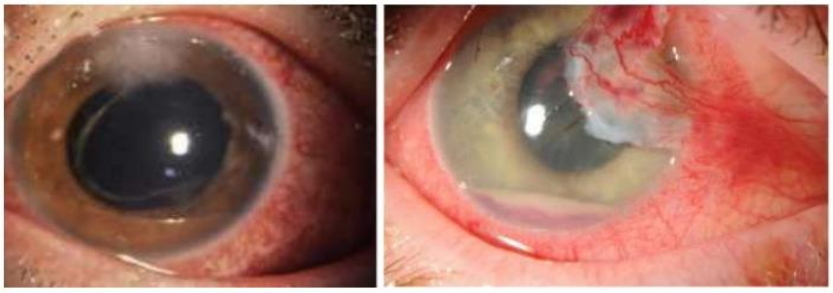
An inflammation of the cornea's layers is known as keratitis. It is frequently linked to bacterial or viral germs that enter the corneal stroma and cause inflammation before eventually destroying these structures. Fungi continue to be one of the most elusive and difficult to diagnose and treat among the organisms that cause keratitis. Additionally, it has been demonstrated that fungal keratitis (FK) infections might be more dangerous and pathogenic than bacterial infections.Monocular blindness and other eye impairments are most commonly caused by a fungus called keratitis, which infects the cornea. Antifungal medications fall into two categories: azoles (voriconazole, ketoconazole, and fluconazole) and polyenes (natamycin). The overall clinical picture of cornea infection includes acute pain, decreased vision, particularly in sunshine, and corneal surface inflammation. In every case during the studies of patients with FK infection, certain symptoms were noted. FK specifically entails

the following: alteration in color of the corneal epithelium with the appearance of ulcers on the surface, invasion of the intact epithelial layer, invasion of the stroma, inflammation, and the presence of fungal hyphae visible on the cornea[10]

Cases of fungal keratitis

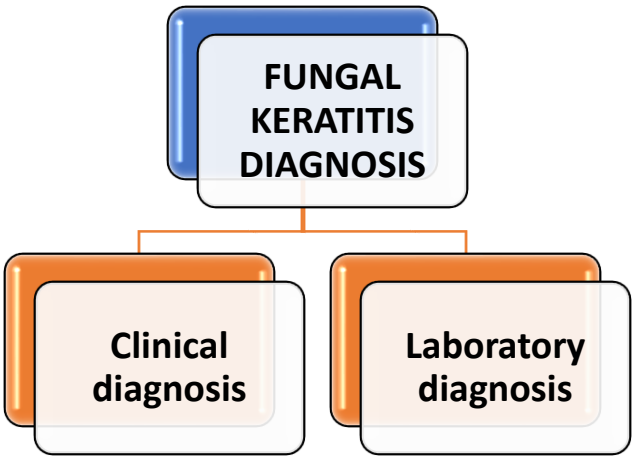
a. Corneal infection caused by Aspergillus fungi

b. Corneal infection caused by Candida Dubliners

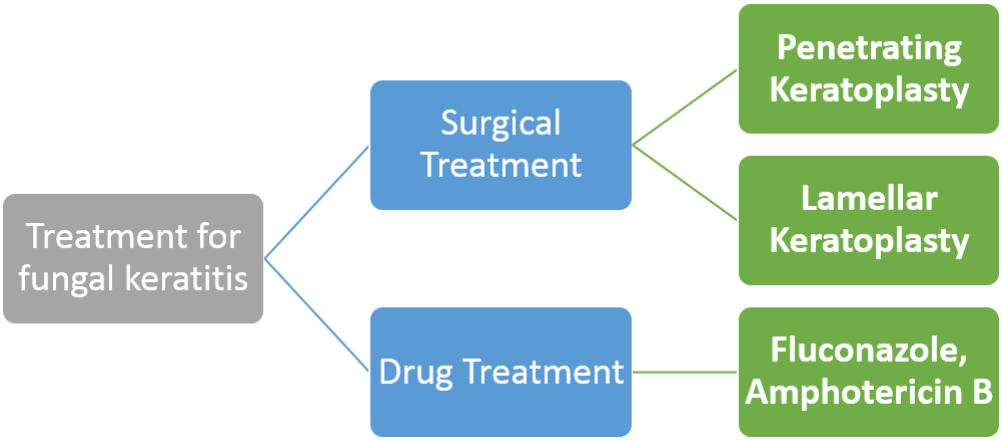


a) b)

ADVANCE DIAGNOSIS OF FUNGAL KERATITIS



TREATMENT OF FUNGAL KERATITIS



DRUG TREATMENT

The closeness between fungus and animal (human) cells is the main barrier to creating an effective antifungal. Ergosterol, the primary sterol in fungal cells, is remarkably similar to cholesterol and serves as the major membrane sterol in human cells. Antifungals therefore focus on targets that are unique to these two cell types. Some commercially available antifungals frequently target RNA production, fungal cell membrane, and cell wall components.[11]

Amphotericin B

The main member of this class, amphotericin, was first discovered in a strain of Streptomyces no do sus in around 1955. Most yeasts and filamentous fungi, including Candida sp., Aspergillus sp., and Cryptococcus sp., are affected by this medication. Amphotericin B is produced for intravenous administration, and hepatotoxicity and nephrotoxicity are the most often reported adverse effects in patients. Studies that try to improve solubility and reduce toxicity, for instance through liposome formulations, have focused on these qualities.

Nystatin

The polyene known as nystatin was first isolated from the Gram-positive bacterium Streptomyces nurse in 1950. This medication is frequently used to treat infections brought on by C. albicans since it has fungicidal and fungistatic properties. This medication is frequently used to treat yeast and fungal infections because it is safe for people.[12]

Fluconazole

Fluconazole is effective in treating a variety of infections, including Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides imcites, Blastomyces dermatitidis, Paracoccidioides Brasiliense's, Separatrix Schenkel, and Penicillium marneffei. Candida species include C. albicans, C. tropicalis, C. glabrata, and C. parap Due to its hydrophilic qualities, it can be used both orally and parenterally and is often easily absorbed by the gastrointestinal tract.[13]

Ketoconazole

The first effective broad-spectrum antifungal for treating yeasts and dermatophytes was ketoconazole. Its launch in 1977 marked a significant advancement for the antifungal medication class. It was the sole oral antifungal available in 1980 for the treatment of systemic infections. But soon enough, the drug's side effects became clear, which made it less useful. The use of this medication was discontinued in Europe in 2013 as a result of adverse consequences in patients, including liver damage

Clotrimazole

Because of its effective skin penetration and minimal systemic absorption, the synthetic drug clotrimazole is frequently used to treat skin and vaginal infections. This medication, which predominantly treats infections brought on by C. albicans, also shows efficacy against Gram-positive bacteria.[14]

SURGICAL TREATMENT

In order to address deep and severe fungal infections, patients with disease that is resistant to medical treatment today have the option of surgical surgery. In order to prevent the infection from spreading to other eye regions and worsening the prognosis, it is often performed within 4 weeks of the patient's initial presentation.[15]

Penetrating Keratoplasty

Penetrating keratoplasty is the most common surgical procedure (other than corneal scraping) (PK). In PK, donor corneal grafts are sutured into place after trephines are used to remove corneal ulcers. According to earlier research, PK is a successful choice for treating severe or resistant cases of fungal keratitis.

Lamellar Keratoplasty

Lamellar keratoplasty (LK), a different surgical treatment, may alter the existing surgical management strategy for fungal keratitis, according to new research. In a method known as "selective LK".[16]

Hyaluronic acid based ophthalmology

Numerous uses for HA exist in ophthalmology, both from a conservative and practical standpoint. Due to its viscoelastic characteristics, it is widely employed as the "lubricant" component and frequently makes up the majority of artificial tear formulations, which are used to treat dry eye. It soothes discomfort, hydrates the eye, and makes up for any sodium hyaluronate deficiency in the tear film. It is also significant that the products in which water is replaced with HA does not dilate conjunctival blood vessels, so they can be safely used in winter. HA also plays an important role in ophthalmic surgery It is widely used during operations of the anterior segment of the eye, such as trabeculectomy, cataract removal, glaucoma treatments, refractive surgery, and corneal plastic surgery[17]

Hyaluronic acid based nanocarrier drug delivery system for fungal keratitis

Ocular medication delivery using nanotechnology For the treatment of eye problems, numerous strategies have been used in recent years. One of the strategies now being studied for both anterior and posterior segment drug delivery is nanotechnology-based ophthalmic formulations. Systems based on nanotechnology that have the right particle size can be created to guarantee reduced irritancy, sufficient bioavailability, and compatibility with ocular tissue. For ocular medication administration, a number of nanocarriers have been created, including nanoparticles, nanosuspensions, liposomes, nano micelles, and dendrimers.

Nano micelles

The most popular carrier systems for forming therapeutic compounds into transparent aqueous solutions are nano micelles . Amphiphili compounds are typically used to create these micro micelles. These compounds could be polymeric or surfactant-based**.**

Nanoparticles

Colloidal carriers known as nanoparticles range in size from 10 to 1000 nm. Lipids, proteins, natural or synthetic polymers, such as albumin, sodium alginate, chitosan, poly (lactide-co-glycolide) (PLGA), polylactic acid (PLA), and polycaprolactone are the main components of nanoparticles used for ocular administration. Nanospheres and nanocapsules are two types of drug-loaded nanoparticles.

Liposomes

Liposomes are lipid vesicles that include an aqueous core inside one or more phospholipid bilayers. Liposomes typically range in size from 0.08 to 10.00 m, and they can be divided into three sizes based on the thickness of their phospholipid bilayers: tiny unilamellar vesicles (10-100 nm), big unilamellar vesicles (100-300 nm), and multilamellar vesicles (contains more than one bilayer).[(18)]

Cubosomes

Cubosomes are well-advocated novel, lipid-based nanovesicles for delivering drugs because of their minimal toxicity and wide areas of interface between hydrophobic and hydrophilic regions. They are well-stabilized vesicles that are composed mainly of a lipid material within an outer shell containing a polymer. Recently, they have come to the attention of drug formulators because of their ability to boost the solubility and bioavailability of lipophilic drugs.[(19)]

FUTURE PRESPECTIVE

According to a study, the newly identified role of vitamin D receptor (VDR) in innate immunity may represent a potential therapeutic target for FK. C. albicans mannan extracts in liposomes stimulate the creation of antibodies that protect mice against candidiasis. Probiotics including Lactobacillus rhamnosus, Lactobacillus acidophilus, Lactobacillus pyogenes, Lactobacillus casei GG, and Bifidobacterium have been shown to protect against candidiasis in mice by inducing protective immunological and non-immune responses. These experimental investigations may help advance efforts to create a vaccination against fungal keratitis and use probiotics on the ocular surface to prevent illness.[(20,21)]

II. CONCLUSION

HA is commonly used polymer in ocular drug delivery, due to its good biocompatibility, adhesion and rheological properties, which can be coupled with drugs and used as a substrate and surface modified drug carrier for drug delivery. In recent years Nanocarriers have attracted importance in the field of topical ocular drug delivery due to resolved the many issues like residence time of corneal surface, interaction with ocular surface, solubility, stability, permeability and bioavailability of drug substance. In this review we have clearly discussed that different type of nanocarrier system with Hyaluronic acid based ocular drug delivery system for fungal keratitis on to fabricate with different excipient having an altered dosage form properties like structure, composition, surface charge of nanocarrier are the important features for corneal interaction and transport system. The collected data evidently showed that nanocarrier system with Hyaluronic acid based ocular drug delivery system is a safe and potential carrier for the treatment of fungal keratitis.

REFERENCE

[1]. Design principles of ocular drug delivery systems: importance of drug payload, release rate, and material properties Astrid Subrizi1,2 , Eva M. del Amo3 , Viktor Korzhikov-Vlakh4 , Tatiana Tennikova4 , Marika Ruponen1 and Arto Urtti1,4,5.

[2]. Hennessy, A.L. et al. (2011) A video study of drop instillation in both glaucoma and retina patients with visual impairment. Am. J. Ophthalmol. 152, 982—988.

[3]. Maurice, D.M. and Mishima, S. (1984) Ocular pharmacokinetics. Pharmacol. Eye 69 19–16.

[4]. Hyaluronic acid (hyaluronan): a review J. Necas1 , L. Bartosikova1 , P. Brauner2 , J. Kolar2 1 Faculty of Medicine and Dentistry, Palacky University, Olomouc, Czech Republic 2 Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic.

[5]. Wu, J., Zhang, Y., Xin, Z. and Wu, X., 2015. The crosstalk between TLR2 and NOD2 in Aspergillus fumigatus keratitis. Molecular Immunology, 64(2), pp.235-243.

[6]. Ledbetter, E., Irby, N. and Kim, S., 2011. In vivo confocal microscopy of equine fungal keratitis. Veterinary Ophthalmology, 14(1), pp.1-9.

[7]. Dahlgren, M., Lingappan, A. and Wilhelmus K.,2017. The clinical diagnosis of microbial keratitis. Am J Ophthalmol,143, pp. 940 – 944.

[8]. Oostra, T., Schoenfield, L. and Mauger, T., 2018. Candida dubliniensis: A novel cause of fungal keratitis. IDCases, 14, p.e00440.

[9]. Amarnath L.P., Srinivas A., Ramamurthi A. (2006): In vitro hemocompatibility testing of UV-modified hyaluronan hydrogels. Biomaterials, 27, 1416–1424.

[10]. Fungal Keratitis: Recent Advances in Diagnosis and Treatment Suwarna Suman, Arushi Kumar, Indu Saxena and Manoj Kumar.

[11]. . Green WR, Bennett JE, Goos RD. Ocular Penetration of Amphotericin B: A Report of Laboratory Studies and a Case Report of Postsurgical Cephalosporium Endophthalmitis. Arch Ophthalmol. 1965; 73:769–775. [PubMed: 14302507]

[12]. Mahdy RA, Nada WM, Wageh MM. Topical amphotericin B and subconjunctival injection of fluconazole (combination therapy) versus topical amphotericin B (monotherapy) in treatment of keratomycosis. J Ocul Pharmacol Ther. 2010; 26:281–285. [PubMed: 20565316].
[13]. CURRENT APPLICATIONS AND PROSPECTS OF NANOPARTICLES FOR ANTIFUNGAL DRUG DELIVERY Sanam Nami1 , Ali Aghebati-Maleki2 , Leili Aghebati-Maleki3,4.
[14]. Nanotechnology-based strategies for treatment of ocular disease Yuhua Wenga,b , Juan Liub,c , Shubin Jinb,c , Weisheng Guob,c,n , Xingjie Liangb,c,n , Zhongbo Hu.
[15]. Bolard, J. How do the polyene macrolide antibiotics affect the cellular membrane properties? Biochim. Biophys. Acta, 1986, 864(3-4), 257-304.
[16]. Holz, R.W. The effects of the polyene antibiotics nystatin and amphotericin B on thin lipid membranes. Ann. N. Y. Acad. Sci., 1974, 235(0), 469-479.
[17]. Krishnan, R.A.; Pant, T.; Sankaranarayan, S.; Stenberg, J.; Jain, R.; Dandekar, P. Protective nature of low molecular weight chitosan in a chitosan-Amphotericin B nanocomplex - A physicochemical study. Mater. Sci. Eng. C, 2018, 93, 472-482.
[18]. Senna, J.P.; Barradas, T.N.; Cardoso, S.; Castiglione, T.C.; Serpe, M.J.; Silva, K.G.H.E.; Mansur, C.R.E. Dual alginatelipid nanocarriers as oral delivery systems for amphotericin B. Colloids Surf. B Biointerfaces, 2018, 166, 187-194.
[19]. Vanden Bossche, H.; Marichal, P.; Odds, F.C. Molecular mechanisms of drug resistance in fungi. Trends Microbiol., 1994, 2(10), 393-400.
[20]. Ha, K.C.; White, T.C. Effects of azole antifungal drugs on the transition from yeast cells to hyphae in susceptible and resistant isolates of the pathogenic yeast Candida albicans. Antimicrob. Agents Chemother., 1999, 43(4), 763-768.
[21]. Kauffman, C.A.; Pappas, P.G.; McKinsey, D.S.; Greenfield, R.A.; Perfect, J.R.; Cloud, G.A.; Thomas, C.J.; Dismukes, W.E. Treatment of lymphocutaneous and visceral sporotrichosis with fluconazole. Clin. Infect. Dis., 1996, 22(1), 46-50.