Nanotechnology based ocular drug delivery system : A Review

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Abstract :

The term nanotechnology has been most commonly used in many fields of science. Nanotechnology has shown tremendous progress in these fields. Similarly, various nonmaterial, such as Nanoparticles, nanostructures, nanotubes and nanowires, synthesized by different approaches like physical, chemical and biological were also found to have enormous application in biomedical and pharmaceutical fields.Nanotechnology has provided the possibility of delivering drugs to specific cells using Nanoparticles.Nanosystems are an emerging part for this strategy.The present article focus the advantages of Nanotechnology in Occular drug delivery System.

Key Word :Nanotubes,Nanogel,Nanoparticles, liposomes, aqueous humor

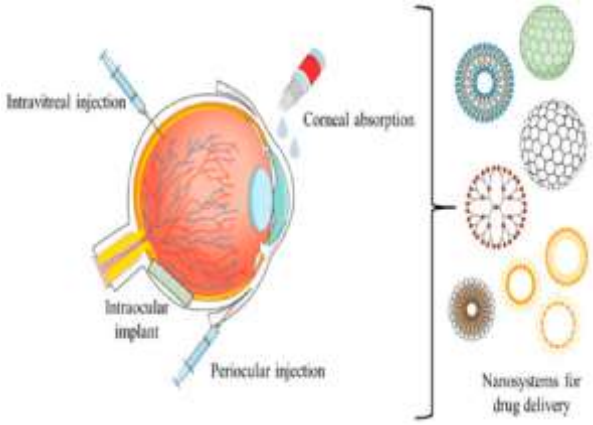
Introduction

The term nanotechnology has been most commonly used in many fields of science. Nanotechnology has shown tremendous progress in these fields. Similarly, various nanomaterials, such as nanoparticles, nanostructures, nanotubes and nanowires, synthesized by different approaches like physical, chemical and biological were also found to have enormous application in biomedical and pharmaceutical fields. It has created a powerful impact in various fields of medicine including cardiology, endocrinology, oncology, immunology, ophthalmology, etc., and to have enormous application in biomedical and pharmaceutical fields. It has created a powerful impact in various fields of medicine including cardiology, endocrinology, oncology, immunology, ophthalmology, etc., and to highly specialized areas, such as gene delivery, brain targeting, tumour targeting and oral vaccine formulations, providing intelligent systems, devices and materials for improved pharmaceutical applications.[1][2][3][4]

Nanotechnology is the manipulation of matter on the atomic, molecular and supramolecular scales (Horikoshi&Serpone, 2013). The nanoscience is not a recent terminology, many nano-molecules are already commonly available in nature, for instance, DNA, water molecules, virus, etc. [5]

Ocular diseases directly affect human vision and quality of life. A survey from 39 countries estimated that 285 million people suffer visual impairment. Of these, 65% are over 50 years old, and 82% of blind patients are over 50 [6]. Significant achievements have been made in the discovery of ocular pathological mechanisms and management of ocular disease. 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.[7]Therefore, the development of improved diagnostics and therapeutics for ocular diseases

receiving intense attention.



Nanotechnology in therapy:

Nanomedicine is the medical application of nanotechnology. Nanomedicine ranges from the medical applications of nanomaterials and biological devices, to nanoelectronic biosensors, and even possible future applications of molecular nanotechnology such as biological machines. Current problems for nanomedicine involve understanding the issues related to toxicity and environmental impact of nanoscale materials (materials whose structure is on the scale of nanometers, i.e. billionths of a meter).[8][9]

Nanotechnology has provided the possibility of delivering drugs to specific cells using nanoparticles.[10] The overall drug consumption and side-effects may be lowered significantly by depositing the active agent in the morbid region only and in no higher dose than needed. Targeted drug delivery is intended to reduce the side effects of drugs with concomitant decreases in consumption and treatment expenses.A benefit of using nanoscale for medical technologies is that smaller devices are less invasive and can possibly be implanted inside the body, plus biochemical reaction times are much shorter. These devices are faster and more sensitive than typical drug delivery. [11]The efficacy of drug delivery through nanomedicine is largely based upon: a) efficient encapsulation of the drugs, b) successful delivery of drug to the targeted region of the body, and c) successful release of the drug.[12]

A number of nanocarriers, including polymeric nanoparticles, micelles, liposomes, and polymer–drug conjugates, among others, have been developed to deliver drugs for various therapeutic applications. The materials that constitute these systems are often decorated with targeting moieties and imaging tags to aid in the delivery of therapeutic payloads to target tissues. An ideal nanocarrier for ocular delivery should meet several criteria in order to achieve an optimal outcome. For example, particle size should be small to minimize irritation. Moreover, the nanocarrier itself should be sufficiently bioavailable to provide adequate treatment. It should ideally be in a suspension form to ensure high therapeutic efficacy, and it should be either biodegradable or biocompatible to avoid producing unwanted side effects such as cytotoxicity.[13]

Nanoparticles have been typically administered via intravitreal injections into the eye. However, this procedure is invasive and has a high degree of risk. An alternative that satisfies the need for less invasive and safer delivery methods is to combine nanotechnology with contact lenses, which are commonplace devices used by millions of people every day.[14]

Polymeric micelles are nanoparticles that self-assemble as a result of amphiphilic interactions.[15] An important characteristic of micelles is their core–shell structure. The core contains the hydrophobic constituents of the nanoparticle matrix and typically constitutes the depot for therapeutic drug, whereas the hydrophilic shell provides interactions with solvents, thereby stabilizing and prolonging the half-life of the therapeutic drug.[16][17] Furthermore, polymeric micelles are biodegradable and biocompatible, thus preventing adverse effects. Polymeric micelles have attracted considerable interest in the drug-delivery field and offer a number of benefits in ocular delivery.

Microemulsions have proven to be an interesting alternative because of their intrinsic properties and specific structures. Microemulsions are clear, stable mixtures of water, oil, and surfactant in combination with a cosurfactant to help stabilize the system.[18][19] They can be administered in suspensions, whereby they help minimize the limitations presented by typical eye drops. When so administered, the presence of surfactant and

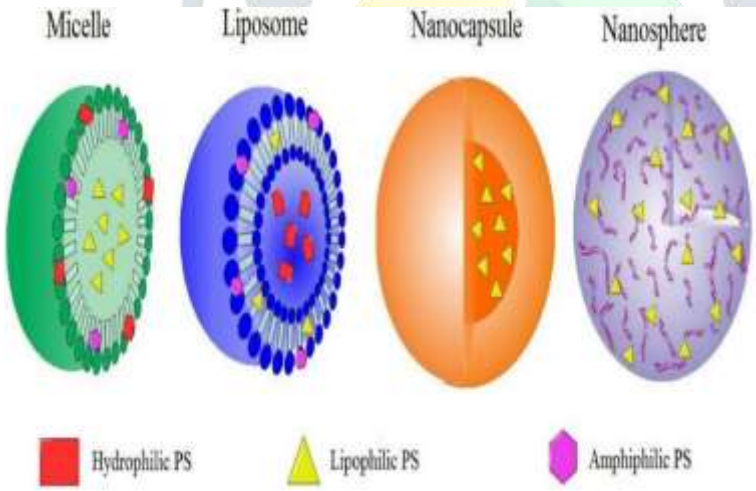
cosurfactant molecules enhances membrane permeability, thereby increasing drug uptake and passage through the corneal membrane.

Liposomes are composed of a lipid bilayer and function as artificial vesicles. Liposomes have a biphasic nature reflected in their lipophilic lipid bilayer and hydrophilic interior aqueous compartment.Liposomes have shown enhancement in precorneal retention, sustained drug release, and transcorneal permeation. liposomes can encapsulate hydrophilic and/or lipophilic therapeutic agents.[20] The surface charge of liposomes is a characteristic of special importance to the cornea. The corneal surface is negatively charged and therefore favors positively charged liposomes over negatively charged and neutral liposomes. Moreover, current research suggests that absorption of encapsulated drugs across corneal membranes can be enhanced by positively charged liposomes.[21]

Dendrimers are nanometer-size, three-dimensional, hyperbranched, monodisperse, multifunctional macromolecular structures.Dendrimers, which are typically 1–10 nm in size, are effective therapeutic drug ccarriersfor various reasons.

Cyclodextrins (CDs) are a series of cyclic oligosaccharides capable of forming inclusion complexes with therapeutic drugs, thus improving their pharmacokinetic properties.[22][23] Ophthalmic formulations co-administered with CDs enhance corneal penetration, ocular absorption, and efficacy of poorly water-soluble drugs, such as dexamethasone, cyclosporin, and acetazolamide. Moreover, cytotoxicity studies have shown that orally administered CDs are practically nontoxic.[24]

Gold and silver nanoparticles (Au-NPs and Ag-NPs respectively) conjugated with a heparin derivative have demonstrated efficacy as anti-angiogenesis agents.[25] Studies of both cancer- and ocular-therapy applications have shown that Au-NPs and Ag-NPs conjugated with a heparin derivative are effectively delivered to their target, where they bind VEGF receptors to inhibit the actions of VEGF via different signaling pathways and ultimately inhibit angiogenesis. Thus, both Au-NPs and Ag-NPs conjugated with antiangiogenic factors clearly have antiangiogenic properties that make them excellent candidates for biomedical use.



Nanogel and properties of nanogels:

The term 'nanogels' defined as the nanosized particles formed by physically or chemically crosslinked polymer networks that is swell in a good solvent. The term "nanogel" (NanoGel™) was first introduced to define cross-linked bifunctional networks of a polyion and a nonionic polymer for delivery of polynucleotides (cross-linked polyethyleneimine (PEI) and poly (ethylene glycol) (PEG).

Nanogels provided a new mean of drug delivery for poorly soluble drugs which doesn't only improve their solubility and stability but increasing the opportunity of their cellular uptake than the free drug [26]. Since they reflect a high affinity to aqueous solution, an outstanding stability, inertness in the systemic as well as the internal fluids ,and appropriateness for molecular in bulk, they are considered promising carriers for delivery and cellular uptake of proteins, peptides and other biological compounds [27].

Biocompatiblity and degradability: Nanogel is made up of either natural or synthetic polymers. They are highly biocompatible and biodegradable thereby avoiding its accumulation in the organs. Chitosan, ethyl cellulose, methyl cellulose and various polysaccharide-based polymers like dextran, pullulan and dextrin can be used to prepare the nanogel. Polysaccharides are mostly carbohydrate-based polymers, formed of repeating monosaccharide units linked by glycosidic bonds. These polymers are stable, non-toxic, hydrophilic and biodegradable in nature.[28]

Swelling property in aqueous media:The most beneficial feature of Nanogels is their rapid swelling/de-swelling characteristics. It is considered to be the fundamental property influencing the mechanism of action followed by this drug delivery system. It depends on: • The structure of Nanogels: This includes the Polymer chain's chemical nature as well as cross-linking degree and in case of polyelectrolyte gels; the charge density.

• Environmental parameters which are related to the variables of the aqueous medium. For instance, in polyelectrolyte gels pH as well as ionic strength and ions' chemical nature areinfluential factors. Likewise, temperature is a trigger of swelling in case of thermoresponsive gels.[29]

Higher drug loading capacity:The properties of higher drug loading capacity of nanogels depend on the functional group present in the polymeric unit. These functional groups have a tremendous effect on drugcarrying and drug-releasing properties, and some functional groups have the potential to conjugate with drugs/antibodies for targeting applications. These pendent functional groups of polymeric chains contribute toward establishing hydrogen bonding or van der Waals forces of interactions within the gel network and thus facilitate the drug-carrying efficiency. Moreover, the presence of functional groups at interface with drug/protein molecules is also responsible for higher loading.

Permeability and particle size:Whatdistinguishesnanodelivery systems is that atiny manipulation in particle size, surface charge and hydrophobicity can remarkably improve permeability. In spite of the fact thatnanoparticles are capable of permeation by diffusion through tissues or compromised areas of endothelium and in some cases through a particular transport system, they created a challenge crossing Blood Brain Barrier (BBB) [28].

Nanogels typically range in size of 20–200 nm in diameter and hence are effective in avoiding the rapid renal exclusion but are small enough to avoid the uptake by the reticuloendothelial system . Good permeation capabilities due to extreme small size. More specifically, it can cross the blood brain barrier (BBB).

Non-immunologicresponse:: Any agent that enters systemic circulation is rapidly eliminated by the Mononuclear Phagocyte System through opsonization and phagocytosis. Opsonization is nothing but marking foreign agents and make them visible to phagocytes. Opsonins bind on the surface of nanoparticles and facilitate the attachment of phagocytes. Few methods are adopted to help nanoparticles flee recognition and remain longer in bloodstream. All of which are based on minimizing protein binding. For example, hydrophilic polymers can act as a shield that hinders or delays binding with opsonins rendering them unnoticeable by immune system and its defences.[28,30]

Colloidal stability:

When handling nanoparticles,there is always a propensity of aggregation that compromises the colloidal stability. Formulators tend to alter the surface charge to avoid the formation of aggregates in bloodstream and further complications. It can be achieved through increasing zeta potential (minimum of ± 30 mV) that results in larger repulsive forces between particles that electrostatically stabilize them. Other techniques involve the incorporation of a surface modifier like PEG that produce steric effects and hydration forces to give a stable nanosuspension [28]. If we compare polymeric micellar nanogel systems and surfactant micelles on basis of stability we will ĮnĚ that the former exhibits stability lower critical micelle concentrations, decrease in dissociation rates, and longer retention of loaded drugs. They also have a high water content that assure good dispersion stability. [30]

Solubility:

Nanogels are able to solubilize hydrophobic drugs and diagnostic agents in their core or networks of gel.

Electromobility:

Nanogels could be prepared without employing energy or harsh conditions such as sonication or homogenization, which is critical for encapsulating biomacromolecules.

Advantages of Nanogel:

Nanogels are considered advantageous over other drug delivery systems for a number of reasons, including:

1. High biocompatibility, which makes nanogels a very promising approach to drug delivery systems [30].

2. High biodegradability, which is crucial to avoid accumulation of nanogel material in the bodily organs, thereby leading to toxicity and adverse effects. [28]

3. Nanogels are inert in the blood stream and the internal aqueous environment, meaning that they do not induce any immunological responses in the body [31].

4. Extremely small size, which induces a number of effects such as:

• Enhanced permeation capability [30].

• Avoidance of rapid renal exclusion. Escaping renal clearance leads to prolonged serum half-life [9]. • Avoidance of clearance by phagocytic cells and the uptake by reticuloendothelial system, which permits both passive and active drug targeting [30]

. • Capability to cross the Blood Brain Barrier [30].

• Safe delivery of drug carrying nanogel particles into the cytoplasm of target cells, therefore making them ideal for intracellular drug delivery.

1.Nanogels are administered via a variety of routes including oral, pulmonary, nasal, parenteral, intra-ocular and topical routes of administration.

2. Nanogels are suitable to administer both hydrophilic and hydrophobic drugs, as well as charged solutes and other diagnostic agents. This property is highly influenced by the type of functional groups present in the network of polymer chains, the crosslinking density and the type of crosslinking agent incorporated in the polymeric network [30].

3. Nanogels have a high affinity to aqueous solutions in their ability to swell or deswell, imbibing water when placed in an aqueous medium. This is the most beneficial characteristics of nanogels as it makes them ideal candidates for the uptake and delivery of proteins, peptides, bio-macromolecules as well as bulky drugs [31].

4. Drug loading in nanogels is relatively high when compared to other nanocarriers and drug delivery systems. This is due to the effectof the functional groups present in the polymeric network. By forming hydrogen bonds or other weak linkages within the polymeric network and interacting with drug or protein molecules at the interface, functional groups on the polymeric network tremendously increase the drug loading capacity of nanogels.

5. Incorporating drug into the nanogels is easy, spontaneous, and does not necessarily require any chemical reactions. This makes the process of preparing nanogels efficient, since the drug is not needed in the initial steps of the manufacturing process and can be introduced to the nanogel network in subsequent steps when the nanogel swell with water or aqueous biological fluids[32].

6. Nanogels are prepared to be capable of releasing drug in a controlled and sustained pattern at the target site, thereby enhancing the therapeutic efficacy of the drug and avoiding its adverse reactions[30].

7.The synthesis of nanogels is generally a stress-free process since mechanical energy is not employed and harsh conditions like sonication or homogenization are not involved [30]. Also, there is no introduction of organic solvents to the process in any of its steps. Hence the drug can be easily loaded without being exposed to any sort of vigorous conditions throughout the preparation process [32].

8. Nanogel dispersions are known to have andexceptionallylarge surface area which is essential for a variety of in vivo application. [32].

9. Bio-macromolecules as well as delicate compounds with low or high molecular weights can be successfully and efficiently encapsulated in the nanogels for the purpose of prolonging the activity of these molecules in the biological environment [32].

10.. Nanogels can be formulated in the form of polymeric micellar nanogel systems that exhibit slower rates of dissociation,better stability over the surfactant micelles, lower critical micelle concentration and, most importantly, longer retention of loaded drugs [30].

Drug Releasing Mechanism of Nanogel:

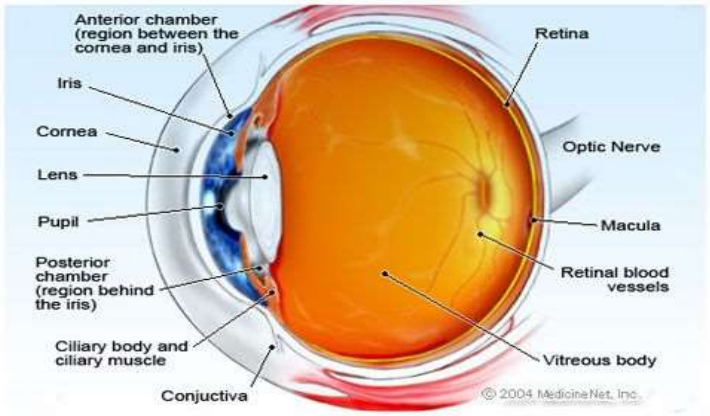
There are multiple mechanisms to which the release of the drug or the biomolecule is attributed to including: simple diffusion,degradationof nanogel structure, pH and temperature changes, counterion displacement or induced due to external energy source [29].

pH responsive mechanism: As the name indicates, drug release responds to pH changes in the surrounding environment. In other words, the release of drug can take place in different physiological environments that acquire different pH values. The most release will take place in the appropriate pH which means that the release is mainly achieved in a targeted area of the body that possesses that pH. This mechanism is based on the fact that polymers employed in the synthesis of a nanogel contain pH sensitive groups that deionize in the polymeric network. The deprotonation results in increase in osmotic pressure, swelling and porosity of the polymer which triggers the release of the electrostatically bound molecules [29,33].

Thermosensitive and volume transition mechanism: Some nanogels are reactive to a specific temperature known as volume phase transition temperature (VPTT) which means they display a change in volume according to the temperature. If the surrounding medium is below VPTT, the polymer becomes quenched and hydrated which makes it swell and release the drug loaded. Above VPTT the opposite occurs and the nanogel shrinks abruptly and the content flows out [34]. Previously, the thermoresponsive nanogels used to rupture cellular network when they expand and increase in volume. So, some alterations were applied on thermosensitive drug-containing nanogels like changing the polymers ratio to achieve lower critical solution temperature.

Photochemical Internalization andPhotoisomerization:Photoisomerization refers to a process in which a bond of restricted rotation undergoes some confirmational changes due to exposure to light. Double bond containing molecules are good example; they isomerize usually from a trans orientation to cis orientation upon light irradiation [36]. When photosensitizers loaded nanogel are excited, they produce two species of oxygen (singlet and reactive) which can result in oxidation in the cellular compartment walls that highly influence the release of therapeutic agents into the cytoplasm [36]. Azodextran nanogel loaded with aspirin was a subject of release studies. The observations showed that Cis-trans isomerization of azobenzene by photoregulation causes the formation of E-configuration of azo group.This results in better release profile of aspirin compared to the previous Z-configuration.[36,35,37]

Introduction to Eye:



The eye is a unique organ, both anatomically and physiologically, containing several widely varied structures with independent physiological functions that render the organ highly impervious to foreign substances. For example, the cornea and the crystalline lens are the only tissues in the body besides cartilage that have no blood supply. This complexity of the eye provides unique challenges to drug delivery strategies in front of the pharmaceutical scientist.[39]

Eye is most interesting organ due to its drug disposition characteristics. Generally, topical application of drugs is the method of choice under most circumstances because of its convenience and safety for ophthalmic chemotherapy .[38]

THE ANATOMY OF THE EYE: The human eye, elegant in its detail and design, represents a gateway to the process we call vision. The eyeball is spherical in shape and about 1 inch across. It houses many structures that work together to facilitate sight. The human eye is comprised of layers and internal structures, each of which performs distinct functions.

A. Sclera: The sclera (white portion of the eye) is the tough white sheath that forms the outer-layer of the ball. It is a firm fibrous membrane that maintains the shape of the eye as an approximately globe shape. It is much thicker towards the back/posterior aspect of the eye than towards the front/anterior of the eye [40]

B. Conjunctiva:The conjunctiva is a thin transparent mucous epithelial barrier, lines the inside of the eyelids, and covers the anterior one-third of the eyeball. The respective portion of conjunctiva is referred to as the palpebral and bulbar conjunctiva. The conjunctiva is composed of two layers: an outer epithelium and its underlying stroma (substantia propria). The exposed surface of the eye includes conjunctiva and cornea and is covered with the tear film. The conjunctiva contributes to the formation of the tear film by way of secreting substantial electrolytes, fluid, and mucins.

C. Cornea: The cornea is a strong clear bulge located at the front of the eye. Surface of the adult cornea has a radius of approximately 8mm. It has an important optical function as it refracts light entering the eye which then passes through the pupil and onto the lens (which then focuses the light onto the retina). The cornea, a non-vascular structure (does not contain any blood vessels) gets the necessary nutrients from the capillaries that terminate in loops at its circumference. It is supplied by many nerves derived from the ciliary nerves. These enter the laminated tissue of the cornea. It is therefore extremely sensitive.

D. Aqueous humor: The aqueous humor is a jelly-like substance located in the outer/front chamber of the eye. It is a watery fluid that fills the "anterior chamber of the eye" which is located immediately behind the cornea and in front of the lens. The aqueous humor is very slightly alkaline salt solution that includes tiny quantities of sodium and chloride ions. It is continuously produced, mainly by the ciliary processes, flows from the posterior chamber through the pupil into the anterior chamber, and exits via the trabecular route at the angle and the uveoscleral route. Schlemm's canal (canal of Schlemm or the scleral venous sinus), is a circular channel that collects aqueous humour from the anterior chamber and delivers it into the bloodstream via the anterior ciliary veins. It is located at the junction of the cornea and the sclera. In human, the rate of aqueous humor turnover is approximately 1% - 1.5% of the anterior chamber volume per minute. The rate of aqueous formation is approximately 2.5 µl/min. Aqueous humor consists of pressure dependent and pressure independent pathways. The pressure dependent outflow refers to the trabecular meshwork-schlemm's canal-venous system, while pressure independent outflow refers to any non trabecular outflow and is called as uveoscleral outflow [41]

E. Pupil: Pupil generally appears to be the dark "centre" of the eye, but can be more accurately described as the circular aperture in the centre of the iris through which light passes into the eye. The size of the pupil (and therefore the amount of light that is admitted into the eye) is regulated by the pupillary reflex (also known as the "light reflex").

F. Iris: The iris is a thin circular contractile curtain located in front of the lens but behind the cornea. The iris is a diaphragm of variable size whose function is to adjust the size of the pupil to regulate the amount of light admitted into the eye. It is the coloured part of the eye (shades may vary individually like blue, green, brown, hazel, or grey).

G. Ciliary Muscle: The ciliary muscle is a ring of striated smooth muscles in the eye's middle layer that controls accommodation for viewing objects at varying distances and regulates the flow of aqueous humour into schlemm's canal. The muscle has parasympathetic and sympathetic innervation. Contraction and relaxation of the ciliary muscle alters the curvature of the lens. This process may be described simply as the balance existing at any time between two states: Ciliary Muscle relaxed (This enables the eye to focus on distant objects) and Ciliary Muscle contracted (This enables the eye to focus on near objects).

H. Lens : The lens is a transparent structure enclosed in a thin transparent capsule. It is located behind the pupil of the eye and encircled by the ciliary muscles. It helps to refract light travelling through the eye (which first refracted by the cornea). The lens focuses light into an image on the retina. It is able to do this because the shape of the lens is changed according to the distance from the eye of the object(s) the person is looking at. This adjustment of shape of the lens is called accommodation and is achieved by the contraction and relaxation of the ciliary muscles.

I. Vitreous Humour : The vitreous humour (also known as the vitreous body) is located in the large area that occupies approximately 80% of each eye in the human body. The vitreous humour is a perfectly transparent thin-jelly-like substance that fills the chamber behind the lens of the eye. It is an albuminous fluid enclosed in a delicate transparent membrane called the hyaloid membrane.

J. Retina: The retina is located at the back of the human eye. The retina may bedescribed as the "screen" on which an image is formed by light that has passed into the eye via the cornea, aqueous humour, pupil, lens, and finally the vitreous humour before reaching the retina. The function of the retina is not just to be the screen onto which an image may be formed but also to collect the information contained in that image and transmit it to the brain in a suitable form for use by the body. The retinal "screen" is therefore a lightsensitive structure lining the interior ofthe eye. It contains photosensitive cells (called rods and cones) and their associated nerve fibers that convert the light they detect into nerve impulses that are then sent onto the brain along the optic nerve.

K. Macula: The center of the retina is called the macula. The macula contains a high concentration of photoreceptor cells which convert light into nerve signals. Because of the high concentration of photoreceptors, we are able to see fine details such as newsprint with the macula. At the very center of the macula is the fovea, the site of our sharpest vision.

L. Choroid: The choroid layer is located behind the retina and absorbs unused radiation and nourishes the outer portions of the retina. It is a thin, highly vascular (i.e. it contains blood vessels) membrane that is dark brown in colour and contains a pigment that absorbs excess light and so prevents blurred vision (due to too much light on the retina). The choroid has one of the highest blood flows in the body. The choroid is loosely attached to the inner surface of the sclera by the lamina fusa.

M.Optic Nerve: The optic nerve (a bundle of over 1 million nerve fibers) is responsible for transmitting nerve signals from the eye to the brain. These nerve signals contain information on an image for processing by the brain. The front surface of the optic nerve, which is visible on the retina, is called the optic disk.

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.The both parts have various biological barriers to protect the eye from foreign substances. The anterior portion includes the corneal, iris, lens, and aqueous humor. 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[42,43].

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[44,45,46].

In recent studies, various efflux transporters on epithelial cells were proved to be of importance in preventing permeation of anti-viral and anti-glaucoma drugs16–18. The intraocular environment contains two main barriers: blood– aqueous and blood–retina barrier. The blood–aqueous barrier is composed of the nonpigmented epithelium of the ciliary body, which specifically includes the iris epithelium, iris vessel endothelium with tight junction, and Schlemm's canal endothelium. The tight junctions of cells control both active and paracellular transport[45,47,48].

The blood–retinal barrier is divided into inner and outer blood–retinal barriers. The former one is composed of retinal vascular endothelium with tight junctions. The latter includes a monolayer of retinal pigment epithelium (RPE) with tight junctions[47,49].

These two components restrict penetration of molecules into the intraocular chamber, resulting in inefficient therapy on intraocular tissues. In addition, topical drug administration to the anterior segment of the eye is often limited by clearance mechanisms of the corneal surface and other precorneal factors, including eye blinking, tear film, tear turnover, solution drainage and lacrimation[50]. Human tear film has a rapid restoration time of only 2–3 min. Thus, most topically administered drugs are washed away within a few seconds after instillation. When topical drug solution volume is more than 30 µL (the upper limit volume that can be accommodated in the cul-de-sac), most of the drug is wasted by either nasolacrimal drainage or gravity-induced drainage[51] Hampered by these factors and ocular barriers, the efficacy of the total administered drugs is less than 5%, suggesting the poor bioavailability of ocular drugs[51,52].

In Situ forming gels for ophthalmic drug delivery

Recently, controlled and sustained drug delivery has become the standard in modern pharmaceutical design and an intensive research has been under taken in achieving much better drug product effective ness reliability and safety.[53]In situ gels are conveniently dropped as a solution into the conjunctival sac, where they underego a transition into a gel with its favourable residence time. The sol-gel transition occurs as a result of a chemical/ physical change induced by physiological environment. This type of gel combines the advantage of a solution being patient convenient with the favourable residence time of a gel for enhancing the ocular bioavailability [54,55].

The sol-gel transition can be induced by a shift in the pH as for cellulose acetate phthalate, a shift in temperature as for the thermogelling Poloxamer 188 or by presence of cations as for deacetylated gellan gum and alginates. Thus, the in situ gelling systems for ophthalmic use can be classified as pH sensitive, temperature sensitive and ion-activated systems. The rate of gel formation in situ, is important since when dropped in the eye, before a strong gel is formed, a solution or a weak gel is prone to elimination by the fluid mechanics of the eye [56].

The ion activated in situ gelling system can be formulated using sodium alginate, the sodium salt of alginic acid, as a natural hydrophilic polysaccharide containing two types of monomers, β-D-mannuronic acid (M) and x-Lguluronic acid (G) which forms a gel in the cul-de-sac due to the presence of divalent calcium ions in the lacrimal fluid [9]. Thus with the use of these in situ gelling systems, residence time of the drug in the eye is increased. Continuous delivery of drugs in a controlled manner to the anterior chamber of the eye will eliminate the requirement for frequent drug administration, causing better patient compliance and will result in extended duration of action, hence lower amount of total dose required, which in turn will minimize the local and/or systemic side effects [57].

Routes of ocular drug delivery system

There are several possible routes of drug delivery into the ocular tissues.The selection of the route of administration depends primarily on the target tissue. Traditionally topical ocular and subconjunctival administrations are used for anterior targets and intravitreal administration for posterior targets. Design of the dosage form can have big influence on the resulting drug concentrations and on the duration of drug action.

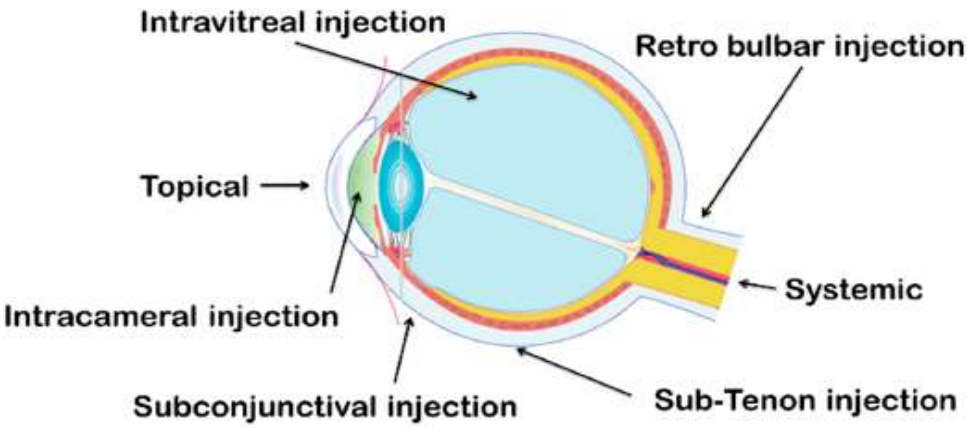
TOPICAL ADMINISTRATION:

Typically topical ocular drug administration is accomplished by eye drops, but they have only a short contact time on the eye surface. The contact, and thereby duration of drug action, can be prolonged by formulation design (e.g. gels, gelifying formulations, ointments, and inserts) [58]. During the short contact of drug on the corneal surface it partitions to the epithelium and in the case of lipophilic compounds it remains in the epithelium and is slowly released to the

corneal stroma and further to the anterior chamber [59]. After eye drop administration the peak concentration in the anterior chamber is reached after 20–30 min, but this concentration is typically two orders ofmagnitude lower than the instilled concentration even for lipophilic compounds [60]. From the aqueous humor the drug has an easy access to the iris and ciliary body, where the drug may bind to melanin. Melanin bound drug may form a reservoir that is released gradually to the surrounding cells, thereby prolonging the drug activity. Distribution to the lens is much slower than the distribution to the uvea [61]. Unlike porous uvea, the lens is tightly packed protein rich structure where drug partitioning takes place slowly. Drug is eliminated from the aqueous humor by two main mechanisms: by aqueous turnover through the chamber angle and Sclemm's canal and by the venous blood flow of the anterior uvea [61].

SUB- CONJUCTIVAL:

Traditionally subconjunctival injections have been used to deliver drugs at increased levels to the uvea. Currently this mode of drug delivery has gained new momentum for various reasons. The progress in materials sciences and pharmaceutical formulation have provided new exciting possibilities to develop controlled release formulations to deliver drugs to the posterior segment and to guide the healing process after surgery (e.g. glaucoma surgery) [62]. Secondly, the development of new therapies for macular degeneration (antibodies, oligonucleotides) must be delivered to the retina and choroid [63,64].
After subconjunctival injection drug must penetrate across sclera which is more permeable than the cornea. Interestingly the scleral permeability is not dependent on drug lipophilicity [65]. In this respect it clearly differs from the cornea and conjunctiva. Even more interesting is the surprisingly high permeability of sclera to the large molecules of even protein size [66]. Thus, it would seem feasible to deliver drugs across sclera to the choroid. However, delivery to the retina is more complicated, because in this case the drug must pass across the choroid and RPE. The role of blood flow is well characterise kinetically but the based on the existing information, there are good reasons to believe that drugs may be cleared significantly to the blood stream in the choroid.



INTRAVITREAL ADMINISTRATION:

Direct drug administration into the vitreous offers distinct advantage of more straightforward access to the vitreous and retina.It should be noted, however, that delivery from the vitreous to the choroid is more complicated due to the hindrance by the RPE barrier. Small molecules are able to diffuse rapidly in the vitreous but the mobility of large molecules, particularly positively charged, is restricted [67]. Likewise, the mobility of the nanoparticles is highly dependent on the structure. In addition to the diffusive movement convection also plays a role [68]. The convection results from the eye movements.

After intravitreal injection the drug is eliminated by two main routes: anterior and posterior [61]. All compounds are able to use the anterior route. This means drug diffusion across the vitreous to the posterior chamber and, thereafter, elimination via aqueous turnover and uveal blood flow. Posterior elimination takes place by permeation across the posterior bloodeye barrier. This requires adequate passive permeability (i.e. small molecular size, lipophilicity) or active transport across these barriers. For these reasons, large molecular weight and water-solubility tend to prolong the half-life in the vitreous [61].

Drugs can be administered to the vitreous also in controlled release formulations (liposomes, microspheres, implants) to prolong the drug activity.

Nanosystem for ocular anterior disease therapy:

Eye drops are the most accessible and common formulations for treatment of common ocular anterior diseases, such as corneal injury, dry-eye, keratitis, conjunctivitis and cataract. However, this route of administration suffers from poor bioavailability due to the corneal barrier and pre-corneal factors. Experimental and clinical research has shown that frequent and long-term use of eye drops can result in tear film instability, corneal surface impairment, and cornea and conjunctiva inflammation[69]. Alternatively, considerable effort is being directed towards prolonging drug retention time on the ocular surface and improving drug penetration. Nanosystems are an emerging part of this strategy. During the past decades, some typical nanosystems have been developed for ocular anterior disease application, as summarized in Table 1.For example, flurbiprofen-loaded PLGA nanoparticles with a size distribution around 200 nm have demonstrated a burst release and an ensuing gradual release profile in vitro. Therapy with this approach showed an improved antiinflammatory effect as compared to commercial flurbiprofen eye drops on the rabbit ocular inflammation model[70]. In addition, flurbiprofen-loaded nanoparticles with a uniform size around 100 nm showed an equivalent inhibitory effect on the miotic response in a rabbit surgical trauma model even at a lower dosage than commercial eye drops. This effect was attributed to the increased release of drugs from the nanoparticles and subsequent penetration into the aqueous humor[71]. Such progress indicates the great impact of colloidal nanocarriers on the enhanced bioavailability of ocular drugs such as flurbiprofen[70,71,72,73]. However, some concerns exist regarding the possible rapid clearance of these formulations from the eye surface. Recently, the in situ gel system is becoming a research hotspot, especially stimuli-responsive hydrogel such as pH-, thermo-, and ion-sensitive hydrogels. Moreover, there are commercial products such as Timoptic-XEs and Virgans, which are ion-activated and pH sensitive hydrogel, respectively. Once the hydrogel is instilled onto the eye surface, the loaded drugs or nanoparticles can escape from the hydrogel upon eye blinking and then release drugs in a sustainable way. Recently, a micellar supramolecular hydrogel was fabricated with methoxy poly (ethylene glycol) block polymer and α-cyclodextrin. In vivo distribution results showed that the hydrogel could significantly enhance penetration and retention of the anti-inflammatory drug diclofenac, as compared with the micelle formulation54. Similar to hydrogel, nanoparticles loaded contact lens is a kind of polymeric nanodevice encapsulated with drugs.Wearers of contact lens can benefit from long drug retention time on the corneal surface[74].

Formulation	Material type	Payload	Size (nm)	Functions	Clinical stage	Ref.
Nanowafer	Polymer	Axitinib	500	The drug loaded nanowafer was nontoxic and could treat corneal neovascularization more efficiently compared to the commercial eye drop even at a lower dosage.	Preclinical	44
Nanoparticle	Chitosan	Gene	~200	The nanoparticle showed superior transfection efficiency in anterior segment of the eye.	Preclinical	45
Hydrogel (Virgan)	Polymer	Ganciclovir	–	Topical treatment drug for herpes simplex virus infection in the eye.	Market	46–49
Nanosuspention	Polymer	Diclofenac	105	Enhanced penetration and retention effect in corneal tissues was achieved through topical administration.	Preclinical	50
Nanoparticle	Polymer	Flurbiprofen	200–300	Following topical administration of the formulation, an enhanced anti-inflammation effect was achieved towards to a built animal model.	Preclinical	51
Nanoparticle	Polymer	Dexamethasone sodium phosphate	100–500	The drug loaded nanoparticles could not cause inflammation in the eye and improved the efficacy for prevention of corneal graft rejection.	Preclinical	52
Nanoscale dispersed oilment	Polymer	–	100	The formulation not only retained the advantages of eye ointment, but also showed better efficacy in repairing the tear film and restoring the corneal surface.	Preclinical	53
Hydrogel	Polymer	Diclofenac	–	The micellar supramolecular hydrogel could extend the retention time on corneal surface and improve drug bioavailability in the eye.	Preclinical	54
Nanoparticle	Polymer	Flurbiprofen	100	Nanoparticle formulation showed an inhibition effect of miotic response in a rabbit trauma model with a lower concentration of drugs. More drugs from the nanoparticles penetrated into the aqueous humor compared to commercial eye drops.	Preclinical	55
Nanoparticle	Polymer	Pilocarpine	83	Studies showed that the duration of miotic response had increased by 40% for the nanoparticle formulation.	Preclinical	56
Liposome	Polymer	Coenzyme-Q10	100–200	The liposomes exhibited a markedly anti-cataract effect and could increase the activities of superoxide dismutase and reduced glutathione.	Preclinical	57

Nanotechnology in ocular disease diagnosis:

There are several approaches employed for clinical ocular disease diagnoses, such as optical coherence tomography (OCT), fundus photography, fluorescein angiography, positron emission.Nanotechnology-based strategies for treatment of ocular disease 287 tomography (PET), magnetic resonance imaging (MRI), ultrasonography and confocal microscopy. They have played a significant role in monitoring disease recovery. For example, MRI is useful for monitoring progress of ocular diseases such as diabetic retinopathy, AMD, and ocular tumor angiogenesis by in vivo imaging of neovascularization[75,76,77]. However, due to poor imaging sensitivity or imaging resolution, each of these

approaches has limited advantages for disease diagnosis. For example, PET has high sensitivity but limited spatial resolution, while MRI has good spatial resolution but low sensitivity[78,79]. In order to overcome these drawbacks, nanotechnology seems to provide multiple options. Anderson et al.[80] developed a Gd-per fluorocarbon nanoparticulate emulsion linked with a biotinylated anti-αvβ3 monoclonal integrin antibody DM101. The system showed a sitedirected contrast enhancement of angiogenic vessels in a rabbit corneal neovasculature model. After administrating the targeted agent for 90 min, the average MRI signal intensity was enhanced by 25% in vivo. Gold nanoparticles are particularly attractive contrast agents for OCT. It is reported that the optical resonance wavelengths of gold nanoparticles can be precisely tuned over a broad range because of their easily controlled sizes and shapes[81] . A typical example was shown upon OCT imaging of phantom samples. Gold nanocages (35 nm edge length) showed a cross section absorption about five orders of magnitude larger than conventional indocyanine green in the near-infrared spectral region[82]. Quantum dots have broad excitation spectrum and narrow emission wavelength, which renders them as good choices for tumorimaging[83]. CdSe quantum dots functionalized with targeted peptides could accumulate in tumors by binding tumor blood endothelial cells after intravenous injection[84] . Although nanotechnologies in tumor diagnosis and therapy have been developed and evaluated in recent years, there are only limited studies focusing on ocular disease application. Yet strategies used in other diseases can also guide the treatment and diagnosis in ocular disease. Recently, Hitomietal.[85] developed a hydrogel nanosystem that combined tumor targeting, triggered drug delivery, and phototo-heat conversion together to enable multimodal imaging and also controlled release of therapeutic cargo in human tumor xenografts. In this study, peptide targeted phage particles, heat sensitive–based liposome (HSL), mesoporous silica nanoparticles (MSNPs), and photon-to-heat conversion were integrated into a hydrogel system. The HSL and MSNPs could generate heat after NIR laser illumination. The heat induced release of hydrogel contents and meanwhile the loaded drugs were controlled to release at tumorsite[85]. Techniques referred in this study offered a nanoplatform that allowing design of different formulations with speci fic ligands (such as antibodies, peptides and aptamers) and nanocarriers for different types, size and growth rate tumors. Nanoplatforms referred here exhibited great potential for clinical application or diagnostic therapeutic monitoring and targeted delivery to malignant tumors and ocular diseases.

Conclusion:

The application of nanomedicine represents a huge breakthrough in the above-mentioned fields and assures an encouraging advance in the next decade. Treatments will become more efficient and safer due to the enormous variety of NP design and functionalization. The lists of potential applications progress to the point where the nanocarrier can be customized to best adjust to a certain active ingredient, a specific environment and then provide fitting drug location at the site of action, in a controlled manner. However, it is relevant to mention that NP-based treatments are not perfect and have challenges to conquer. First, the number of polymeric materials currently available for their utilization as DDS is still limited although the R&D has been moved in the last decade, exceeding expectations, from the micro- to the nanosize scale. The ideal adjustment to the delivery conditions, such as transportation to the site of action, specific targeting or adequate delivery profile, among others, for each type of disease, requires the development of new polymers that can fit these requisites. Although selective targeting supposed a great improvement in comparison to non-encapsulated drugs, it is a very complex mechanism and represents a challenge itself. Overexpression of a specific surface protein is not enough to assure selective targeting as they are also normally expressed in normal cells. This point is more critical in cancer treatments, where administered drugs usually possess higher toxicity that could lead to numerous undesirable secondary effects compared to drugs used in other diseases treatments. Most the assays have been developed in small animal models showing promising results, but the translation from animal results into clinical success has been limited. More clinical research and data are needed to fully comprehend the mechanism of these nanocarriers. In addition, limitations include the uncertain future of pharmaceutical companies which face high expenses concerning clinical trials and decreasing success rates in the flow of novel entities in the R&D pipeline.

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