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A Review on Ocular Novel Drug Delivery Systems.

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ABSTRACT
Delivery of drugs to eyes is a great challenge to researchers because of a number of barriers in the eye preventing the actual dose from reaching the site. A number of ophthalmic delivery systems have been developed in the past couple of years that are not only new but also safe and reliable and help to overcome all those barriers in the eye which are responsible for the very less bioavailability of drugs. In this review, we tried to focus on current research in ocular delivery of drug substances giving special emphasis to liposomal delivery system. A brief analysis of other novel ocular delivery systems, ocular physiology, and microbial sources of disease are also highlighted herein. We analyzed the various research findings for churning a general idea for novel ocular delivery system and its future use. The novel formulations may overcome the addressed problems of ophthalmic medication and comply with the quality assurance issues. The liposomal delivery is advantageous as they have the ability to entrap both hydrophobic and hydrophilic drugs and are suitable for delivery to both the anterior and posterior segment of the eye. Therefore, the use of this alternative approach is quite a necessity.

Keywords: Drug delivery, eye diseases, liposome, ocular, ocular physiology.

INTRODUCTION

Delivery of drugs to eye is a great challenge for pharma- ceutical researchers because a number of barriers in the eye prevent the actual dose from reaching the site and also from being maintained in its therapeutic concentration at the location. A number of delivery systems for the eye have been developed in the past couple of years that are not only new but also safe and reliable and help to over- come all those barriers in the eye which are responsible for the very less bioavailability of drugs. The novel drug delivery systems are non-irritant to the eye and produce an enhanced retention time in the eye, thus providing greater efficacy and bioavailability. The liposomal systems for delivery of drugs to eye are advantageous as they have the ability to entrap both hydrophobic and hydrophilic drugs and are suitable for delivery to both the anterior and poste- rior segment of the eye.

Importance of novel drug delivery systems in ocular drug delivery-

The effective delivery of drugs to the eye is still a major challenge to the researchers for the chief reason that the eye offers several physiological barriers, which act as a hindrance, and restrict the ocular delivery of drugs at the desired site. Scientists are focusing upon newer areas of research, in order to further improve and enhance the various drug delivery systems so that the drug may be specifi-cally and suitably delivered at the target site.

The improvements in the field of ocular drug delivery researches are likely to bring about novel methods for bet-ter management of the ocular diseases with newer thera- peutic modalities. These newer systems of drug delivery are expected to deliver a sustained action, and with a method of administration, which has a significantly reduced invasive nature, improved efficiency, and a higher level of safety.

Various novel drug delivery systems for the eye are cur- rently under the process of clinical trials. They have been made in such a manner that the duration of action is enhanced and a sustained release of the drug is thereby obtained. Likewise, many are already available in the mar-ket. Majority of them have been designed in order to com-bat the diseases associated with the posterior segment, which generally affect the eye for a longer period. However, the development of a sustained delivery system for the self-administration by patients, for administration to the posterior segment, still remains a major challenge to the newer technologies, since these areas cannot be easily reached and hence require an invasive treatment by techni-cally trained professionals.

Considering the fact that there exists a room for pro- spective progresses in the areas of effective delivery of drugs and diagnostics, numerous benefits are still provided in the field of nanotechnology, as it allows not only an enhanced site-specific delivery of drugs but also a release of

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the drug in a controlled manner. And, the sole purpose for this site-specific delivery of drugs, as well as its release in a controlled manner, is mainly to achieve an improved pharmacokinetics and pharmacodynamics profile of the drug, to reduce the associated toxicity at the site, and for a better immunogenicity and recognition of the system within the body, for an enhanced therapeutic efficacy.

In studies, researchers found that highest bioavailability is produced by lipophilic compounds that have a high per- meability in the cornea. The volume does not affect the bioavailability for those therapeutic moieties, which have a high permeability in the cornea. For drugs that have a low corneal permeability, if the dosage volume is consid- erably reduced, an improvement in the bioavailability of

~4 can be achieved.[4] Researchers have found that α-cyclodextrin cysteamine acts as a promising tool for enhancing the retention time of therapeutic moieties on the mucosa of eye.

Ocular anatomy and physiology-

The understanding of ocular anatomy and physiology is very essential before designing a drug delivery system for the eye. Human eye is a very small, yet, sensitive organ, which poses numerous challenges and barriers, for the effective delivery of drugs. Basically, the human eye can be roughly divided into two major segments: (a) anterior segment and (b) posterior segment. If the entire eye is con- sidered to be constituted of three parts, then the first one- third portion will be of that consumed by the anterior segment, while the remaining two-third portion will be of that consumed by the posterior segment:

Anterior segment is the exterior part of the eye, which forms the outer surface. It is positioned in front of the vitreous humor. It mainly consists of structures like cornea, pupil, conjunctiva, ciliary body, lens, aqueous humor, and iris.

Posterior segment is the part of the eye, which lies behind and cannot be viewed directly. It forms the interior structure of the eye. The posterior segment consists mainly of the sclera, retinal pigment epi- thelium, choroid, neural retina, vitreous humor, macula, and optical nerve.

For efficient ocular delivery, the drug must overcome the major barriers offered by the eye, in order to protect the eye from the toxicants. These barriers of the eye are spe- cific to the site, depending upon the route of administra- tion of drugs. Barriers to ocular delivery of drugs may be broadly classified into three major types: (a) precorneal barrier, (b) static barriers, and (c) dynamic barriers:

Static barriers of the eye are mainly the various lay- ers of the cornea, sclera, and the retina, inclusive of the blood-aqueous barrier as well as the blood-reti- nal barrier.

Dynamic barriers offered by the eye are mainly the choroidal and the conjunctival blood flow, dilution of tears, and the lymphatic clearance.

Anterior segment of the eye may be affected by certain diseases like glaucoma, allergic conjunctivitis, anterior uveitis, and cataract, in addition to numerous other diseases.

Posterior segment of the eye is mainly affected by dis- eases, the main causative factor of which is limited to age. The diseases of the posterior segment of the eye are a pre- dominant reason for causing visual impairment in the indus- trialized nations of the world. Examples of diseases affecting the posterior segment of the eye are age-related macular degradation (AMD), diabetic retinopathy, and so on. A schematic diagram of human eye is shown in Figure 1.

Eye as a site of infection

The eye is a very sensitive organ, vulnerable to many infections. The causative agents for infecting the eyes mayrange from microbes such as bacteria, viruses, fungi, and even parasites. Based on the cause and type of infection, treatment may be given using anti-bacterials, anti-fungals, antiseptics, anti-virals, anti-helminths, and so on. Infection of the eye with such microbes may threaten normal vision.

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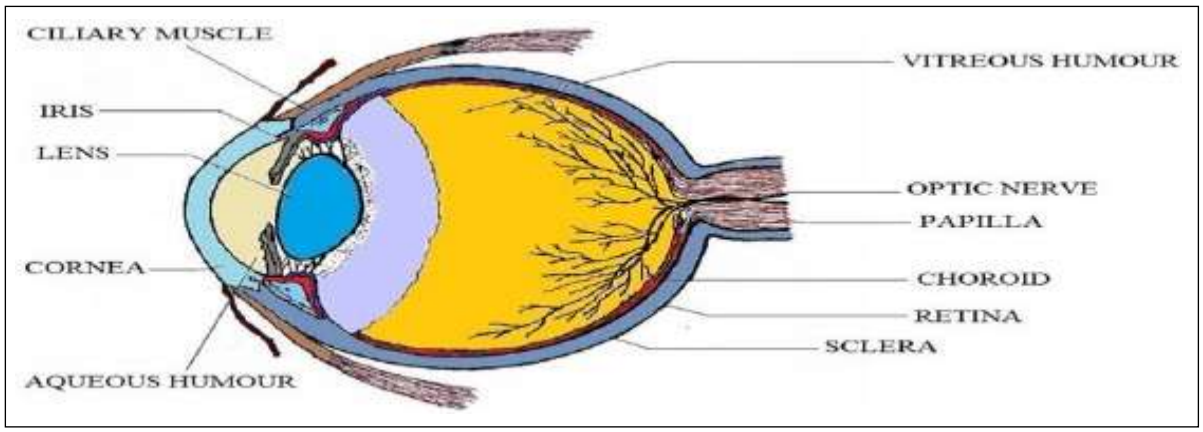

Figure 1. Schematic diagram of human eye.

Such infections occur, when the microbes get transmitted to the eye, either during birth or from the environment, and invade the conjunctiva, eye-lids, and other vulnerable ocu- lar tissues, with a potential of becoming pathogenic.

The source of infections is basically the microbes and may spread from an infected person, following unhygienic practices, and so on. Although the infections may occur inanyone's eye, however, there is always a certain group in the population, who are most susceptible to such infections:

Diseases like bacterial conjunctivitis are most susceptible in pre-school and school-going children, with chances of epidemic occurrence.

Keratitis is mostly susceptible in those patients, whose corneal epithelium has been compromised because of previous injury or trauma, due to which rapid ulceration may be caused, and inflammatory cells infiltration may occur.

Hyperacute bacterial conjunctivitis and chlamydial conjunctivitis may be caused in both neonates and adults. But, in the latter, it is associated with genitourinary discharge as well as dysuria.

Immuno-compromised patients, particularly those suffering from AIDS, are susceptible to severe and rapidly progressive uveitis due to cytomegalovirus.

According to findings, patients suffering from endoge- nous ophthalmitis due to Klebsiella spp. have been found to be suffering from diabetes too.

Novel drug delivery systems forocular therapy

Novel drug delivery system is required for ocular delivery of drugs because the conventional ocular dosage forms suffer from numerous disadvantages. The major problem that is suffered by such conventional therapies is least ocular bioavailability, due to which majority of the drug gets lost, and a minor percentage of it actually reaches the desired site. The reason for this loss is the unique anatomy of the eye and the nature of its tissues. For these reasons, drug delivery to the eye has always remained a major challenge.

If we consider the example of eye drops as a conventional means of drug delivery, we can highlight on the needof novel drug delivery systems for ocular therapy, by exemplifying the disadvantages that are associated with conventional eye drops. The posterior segment of the eye is deprived of treatment using eye drops. Eye drops are known to treat "only" the diseases that are associated with the anterior segment of the eye. In the process, due to draining out of the drops from the eye, the rapid turnover of the tears, blinking, and induction of tears, maximum ofthe drug is lost from the site. Thus, only a meager quantity of less than 5% reaches the intraocular tissues.

The most popular novel methods of drug delivery to theocular space are described as follows.

Niosomes

Niosomes are one of the best among these carriers. The self-assembly of non-ionic surfactants into vesicles was first reported in the 70s by researchers in the cosmetic industry. Niosomes (non-ionic surfactant vesicles) obtained on hydration are microscopic lamellar structures formed upon combining non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class with cholesterol. The non-ionic surfactants form a closed bilayer vesicle in aqueous media based on its amphiphilic nature using some energy for instance heat, physical agitation to form this structure. In the bilayer structure, hydrophobic parts are oriented away from the aqueous solvent, whereas the hydrophilic heads remain in contact with the aqueous solvent. The properties of the vesicles can be changed by varying the composition of the vesicles, size, lamellarity,

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tapped volume, surface charge and concentration. Various forces act inside the vesicle, eg, van der Waals forces among surfactant molecules, repulsive forces emerging from the electrostatic interactions among charged groups of surfactant molecules, entropic repulsive forces of the head groups of surfactants, short-acting repulsive forces, etc. These forces are responsible for maintaining the vesicular structure of niosomes. But, the stability of niosomes are affected by type of surfactant, nature of encapsulated drug, storage temperature, detergents, use of membrane spanning lipids, the interfacial polymerisation of surfactant monomers in situ, inclusion of charged molecule. Due to presence of hydrophilic, amphiphilic and lipophilic moieties in the structure, these can accommodate drug molecules with a wide range of solubility. These may act as a depot, releasing the drug in a controlled manner. The therapeutic performance of the drug molecules can also be improved by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells. Noisome made of alpha , omega-hexadecyl-bis-(1-aza-18-crown-6) (Bola-surfactant)-Span 80-cholesterol (2:3:1 molar ratio) is named as Bola-Surfactant containing noisome. The surfactants used in niosome preparation should be biodegradable, biocompatible and non-immunogenic. A dry product known as proniosomes may be hydrated immediately before use to yield aqueous niosome dispersions. The problems of niosomes such as aggregation, fusion and leaking, and provide additional convenience in transportation, distribution, storage, and dosing.
Niosomes behave in vivo like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability. As with liposomes, the properties of niosomes depend on the composition of the bilayer as well as method of their production. It is reported that the intercalation of cholesterol in the bilayers decreases the entrapment volume during formulation, and thus entrapment efficiency.

In situ gelling system

The solutions of polymers, which undergo transition from sol-gel phase under environmental stimuli to form a visco-elastic gel are referred to as in situ gelling system. The induction of gelation may be caused due to variation in temperature, pH, ions, or irradiation by ultraviolet (UV)- light. For delivery to eye, researchers are showing more interest in developing such in situ gels that respond to tem-perature change.

Grateiri et al. developed an ocular in situ gelling system using poloxamer/chitosan. The formulation of the polox- amer with chitosan in the ratio of 16:1 showed a good ocu- lar retention and exhibited an optimal gelation, and also the ability to resist low force of shear at 35°C. Also, at this temperature, the formulation had an increased hardness value and an increased mucoadhesion.

Liu et al. studied the potential of alginate/hydroxypro- pyl methylcellulose (HPMC)-based in situ gelling formu- lations containing gatifloxacin for ocular delivery. Rheological studies showed that the gatifloxacin as well asblank formulations showed a gradual shear-thinning, with a reduction in viscosity on increasing the angular velocity. Also, viscosity increased considerably after diluting the formulations with artificial tear fluid. Alginate showed a transition to gel phase on being exposed to tear fluid but 2% HPMC E50Lv solution did not. The best formulation contained 1% alginate and 2% HPMC E50Lv and showed good release with no irritancy and tissue damage. irritation in the ocular tissues, ease in formulating it into drops for ophthalmic use, and its sterilization.

A nanosuspension system was developed by Pignatello et al., using Eudragit RS100® for the ocular delivery of ibu- profen (IBU). Their formulation had a mean particle size with a positive charge and showed controlled release. In vivo studies on rabbit's eye induced with miosis showed its inhibition. But, after instillation of the nanosuspension, a high concentration of the free drug did not travel from the system into the conjunctival sac. The aqueous humor of theeye had increased concentration of IBU post application of the formulation, but showed no toxicity or irritancy.

Pignatello et al. constructed polymeric nanoparticle sus- pensions out of Eudragit RS100 and RL100®, which were found biocompatible. Photon correlation spectroscopy stud-ies showed that the particle size for RL as well as RS nano-suspension was low, which was suitable for ocular administration. Furthermore, it showed a diffusional releaseof the drug. Electrophoretic studies also gave good results. Zeta-potential of the nanosuspension revealed its positive charge, thereby enhancing corneal retention time.

Researchers formulated a novel ocular controlled release nanoparticulate suspension system for delivering acyclovir (ACV). The formulations were stable and had a particle size in narrow range, with good EE. In vitro drug release profile depicted its efficiency in releasing the drug

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in a controlled fashion in the eye. In vivo studies revealed that at 8 h, 82.83, 77.49, and 34.15 mg/mL of ACV retained in the aqueous humor.

Nanosuspensions

Nanosuspensions are defined as the submicron colloidal dispersions of pharmaceutical active ingredient particles in a liquid phase, size below 1μm, without any matrix material which are stabilized by surfactants and polymers. 1 Nanosuspensions differ from nanoparticles and solid lipid nanoparticles with respect to the fact that nanoparticles are polymeric colloidal carriers of drug while solid lipid nanoparticles are lipid carrier of drugs. An increasing number of newly developed drugs are poorly soluble; in many cases drugs are poorly soluble in both aqueous and organic media excluding the traditional approaches of overcoming such solubility factors and resulting in bioavailability problems. An alternative and promising approach is the production of drug nanoparticles (i.e. nanosuspensions) to overcome these problems. Nanosuspensions have emerged as a promising strategy for the efficient delivery of hydrophobic drugs because of their versatile features and unique advantages. The unique features of nanosuspensions have enabled their use in various dosage forms, including specialized delivery systems such as mucoadhesive hydrogels. The major advantages of this technology are its general applicability to most drugs and its simplicity. Preparation of nanosuspension is simple and applicable to all drugs which are water insoluble. Nanosuspensions are prepared by using wet mill, high pressure homogenizer, emulsion solvent evaporation, melt emulsification and supercritical fluid techniques. Nano-suspensions can be delivered by oral, parenteral, pulmonary and ocular routes. Nanosuspensions can also be used for targeted drug delivery when incorporated in the ocular inserts and mucoadhesive hydrogels. Currently, efforts are being directed to extending their applications in sitespecific drug delivery. Rapid strides have been made in the delivery of nanosuspensions by parenteral, preoral, ocular and pulmonary routes.

Emulgel

Emulgels may be referred to as those water-in-oil or oil-in- water emulsion formulations, which are converted to a gelby the addition of some gelling agent. They are formed on combination of emulsion and gel, to yield a single formu- lation. They bear the advantages of both emulsion and gel and have good acceptability among patients.

An ocular emulgel system was formulated by Shen et al., using cyclosporine A (CsA). The prepared formulations had acceptable pH and osmotic pressure. Rheological studies confirmed its pseudo-plastic nature, perfect for topical eye formulations. The formulations passed stability tests and were also non-irritant. Drug release of CsA from the emulgel showed best result from the formulation, which contained0.2% polycarbophil.

Liposomes

Liposomes are extensively used as carriers for numerous molecules in cosmetic and pharmaceutical industries. Additionally, food and farming industries have extensively studied the use of liposome encapsulation to grow delivery systems that can entrap unstable compounds (for example, antimicrobials, antioxidants, flavors and bioactive elements) and shield their functionality. Liposomes can trap both hydrophobic and hydrophilic compounds, avoid decomposition of the entrapped combinations, and release the entrapped at designated targets .

Because of their biocompatibility, biodegradability, low toxicity, and aptitude to trap both hydrophilic and lipophilic drugs and simplify site-specific drug delivery to tumor tissues , liposomes have increased rate both as an investigational system and commercially as a drug-delivery system. Many studies have been conducted on liposomes with the goal of decreasing drug toxicity and/or targeting specific cells .

Liposomal encapsulation technology (LET) is the newest delivery technique used by medical investigators to transmit drugs that act as curative promoters to the assured body organs. This form of delivery system proposal targeted the delivery of vital combinations to the body. LET is a method of generating sub-microscopic foams called liposomes, which encapsulate numerous materials. These ‘liposomes’ form a barrier around their contents, which is resistant to enzymes in the mouth and stomach, alkaline solutions, digestive juices, bile salts, and intestinal flora that are generated in the human body, as well as free radicals. The contents of the liposomes are, therefore, protected from oxidation and degradation. This protective phospholipid shield or barrier remains undamaged until the contents of the liposome are delivered to the exact target gland, organ, or system where the contents will be utilized.

Clinical medication keeps an enormously

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broad range of drug molecules at this time in use, and new drugs are added to the list every year. One of the main aims of any cure employing drug is to increase the therapeutic index of the drug while minimizing its side effects. The clinical usefulness of most conservative chemotherapeutics is restricted either by the incapability to deliver therapeutic drug concentrations to the target soft tissue or by Spartan and harmful toxic side effects on normal organs and tissues. Different approaches have been made to overcome these difficulties by providing the 'selective' delivery to the target area; the ideal solution would be to target the drug alone to those cells, tissues, organs that are affected by the disease. Selected carriers, for instance colloidal particulates and molecular conjugates, can be appropriate for this determination. Colloidal particulates result from the physical incorporation of the drug into a particulate colloidal system, for instance reverse micelles, noisome, micro- and nano-spheres, erythrocytes, and polymers and liposomes. Among these carriers, liposomes have been most studied. Their attractiveness lies in their composition, which makes them biodegradable and biocompatible. Liposome involves an aqueous core entrapped by one or more bilayers composed of natural or synthetic lipids. They are composed of natural phospholipids that are biologically inert and feebly immunogenic, and they have low inherent toxicity. Furthermore, drugs with different lipophilicities can be encapsulated into liposomes: strongly lipophilic drugs are entrapped almost totally in the lipid bilayer, intensely hydrophilic drugs are located entirely in the aqueous compartment, and drugs with intermediary logP effortlessly partition between the lipid and aqueous phases, both in the bilayer and in the aqueous core.

Classification of liposomes

The liposome size can vary from very small (0.025 μm) to large (2.5 μm) vesicles. Moreover, liposomes may have one or bilayer membranes. The vesicle size is an acute parameter in determining the circulation half-life of liposomes, and both size and number of bilayers affect the amount of drug encapsulation in the liposomes. On the basis of their size and number of bilayers, liposomes can also be classified into one of two categories:
(1) multilamellar vesicles (MLV) and (2) unilamellar vesicles. Unilamellar vesicles can also be classified into two categories: (1) large unilamellar vesicles (LUV) and (2) small unilamellar vesicles (SUV). In unilamellar liposomes, the vesicle has a single phospholipid bilayer sphere enclosing the aqueous solution. In multilamellar liposomes, vesicles have an onion structure. Classically, several unilamellar vesicles will form on the inside of the other with smaller size, making a multilamellar structure of concentric phospholipid spheres separated by layers of water.

Methods of liposome preparation
General methods of preparation
All the methods of preparing the liposomes involve four basic stages:
1. Drying down lipids from organic solvent.
2. Dispersing the lipid in aqueous media.
3. Purifying the resultant liposome.
4. Analyzing the final product.
Method of liposome preparation and drug loading
The following methods are used for the preparation of liposome:
1. Passive loading techniques
2. Active loading technique.
Passive loading techniques include three different methods:
1. Mechanical dispersion method.
2. Solvent dispersion method.
3. Detergent removal method (removal of non-encapsulated material) .

Mechanical dispersion method
The following are types of mechanical dispersion methods:
1.1. Sonication.
1.2. French pressure cell: extrusion.
1.3. Freeze-thawed liposomes.
1.4. Lipid film hydration by hand shaking, non-hand. shaking or freeze drying.
1.5. Micro-emulsification.
1.6. Membrane extrusion.
1.7. Dried reconstituted vesicles .

Nanoemulsions

Nanoemulsions, also known as submicron emulsions, ultrafine emulsions and miniemulsions, are submicron sized colloidal particulate systems considered as thermodynamically and kinetically stable isotropic dispersions, which consist of two immiscible liquids like water and oil, stabilized by an interfacial film consisting of a suitable surfactant and co-surfactant to form a single phase. A number of surfactants with diverse characteristics (ionic or non-ionic) had been used with such nanoemulsions. Most widely used among them were nonionic surfactants (sorbitan esters, polysorbates), anionic surfactants (potassium

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laurate, sodium lauryl sulphate), cationic surfactants (quaternary ammonium halide) and zwitterions surfactants (quaternary ammonium halide). Early nanoemulsions were oil-in-water (O/W) type emulsions with average droplet diameter ranging from 50 to 1000 nm. Nanoemulsions more recently are classified into three categories such as O/W type (oil is dispersed in aqueous phase), water-in-oil (W/O) type (water is dispersed in oil phase), and bi-continuous (microdomains of water and oil are interdispersed within the system). Transformation among these three types can be attained by altering the components of the emulsions. Multiple emulsions are also a type of nanoemulsions, where both O/W and W/O emulsions present simultaneously in one system. For stabilizing these two emulsions, both hydrophilic and lipophilic surfactants are used simultaneously. Nanoemulsions offer various advantages over other dosage forms and these advantages are, (1) increased rate of absorption, (2) reduced variability in absorption, (3) protection from oxidation and hydrolysis in O/W nanoemulsions, (4) delivery of lipophilic drugs after solubilisation, (5) aqueous dosage form for water insoluble drugs, (6) enhanced bioavailability for many drugs, (7) ability to incorporate both lipophilic and hydrophilic drugs, (8) delivery systems to enhance efficacy while reduce total dose and side effects, (9) as non-toxic and nonirritant vehicles for skin and mucous membrane delivery and (10) release control by permeation of drug through liquid film, whose hydrophilicity or lipophilicity as well as thickness can be precisely controlled.

Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. These are apply a wide spectrum of preparations for both cosmetic and dermatological, to their healthy

Nanoparticle

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. In recent years, biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymer such as poly(ethylene glycol) (PEG) known as long-circulating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period time target a particular organ, as carriers of DNA in gene therapy, and their ability to deliver proteins, peptides and genes 1-4. The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen. Though liposomes have been used as potential carriers with unique advantages including protecting drugs from degradation, targeting to site of action and reduction toxicity or side effects, their applications are limited due to inherent problems such as low encapsulation efficiency, rapid leakage of water-soluble drug in the presence of blood components and poor storage stability. On the other hand, polymeric nanoparticles offer some specific advantages over liposomes. For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties 5, 6. The advantages of using nanoparticles as a drug delivery system include the following:

1. Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.
2. They control and sustain release of the drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug so as to achieve increase in drug therapeutic efficacy and reduction in side effects.
3. Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.
4. Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.
5. The system can be used for various routes of administration including oral, nasal, parenteral, intra-ocular etc. In spite of these advantages, nanoparticles do have limitations.

For example, their small size and large surface area can lead to particleparticle aggregation, making physical handling of nanoparticles difficult in

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liquid and dry forms. In addition, small particles size and large surface area readily result in limited drug loading and burst release. These practical problems have to be overcome before nanoparticles can be used clinically or made commercially available. The present review details the latest development of nanoparticulate drug delivery systems, surface modification issues, drug loading strategies, release control and potential applications of nanoparticles.

Nanogels

These are hydrogels that have sizes in nano-regime, made up of cross-linking of polymer chains. They swell into a considerable volume when dispersed in aqueous medium. Nanogels may be loaded with therapeutic agents by inter- action between agent and functional group present in the polymer either physically or chemically. Nanogels are highly biocompatible, versatile, show a controlled release of drug, and are also able to protect biodegradable mole- cules from degrading inside the body.

Wang et al. prepared muscone containing nanogel for ophthalmic delivery that was self-assembled and thermo-responsive in nature, formulated using reverse micelle □ positive micelle technique. Results demon- strated non-irritancy in eye, and very high loading of muscone, with a phase transition of 34.05°C. Fluorescent labeling technology revealed a better corneal retention of the formulation than muscone eye drops. In vivo and in vitro studies of the formulation showed better bioavailabil- ity and significantly slow release-rate of muscone, but at a considerably faster rate than hydrogels, respectively, in comparison with muscone eye drops.

Nanomicelles-

Nanomicelle consists of amphiphilic molecules that self-assemble in aqueous media to form organized supramolecular structures. Micelles can be prepared in various sizes (10-1000 nm) and shapes conditional on the molecular weights of the core and corona forming blocks. Nanomicelle have been an attractive carrier for their potential to solubilize hydrophobic molecules in aqueous solution 3 . In addition, small size in nanometer range and highly adjustable surface properties have been reported to be advantageous in ocular drug delivery. In this review, various factors influencing rationale design of nanomicelle formulation and disposition are discussed along with case studies. Despite the progress in the field, influence of various properties of nanomicelle such as size, shape, surface charge, rigidity of structure on ocular disposition need to be studied in further details to develop an efficient nanocarrier system 4 . The eye is a complex organ with a unique anatomy and physiology. The structure of eye can be divided into two main parts: anterior segment and posterior segment. Anterior segment of the eye occupies approximately one-third while the remaining portion is occupied by the posterior segment. Tissues such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make up the anterior portion. Back of the eye or posterior segment of the eye include sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor. The anterior and posterior segment of eye is affected by various vision threatening diseases. Diseases affecting anterior segment include, but not limited to glaucoma, allergic conjunctivitis, anterior uveitis and cataract. While, age-related macular degeneration (AMD) and diabetic retinopathy are the most prevalent diseases affecting posterior segment of the eye.

Dendrimers

The macromolecular compounds in which an inner core is surrounded by a series of branches are referred to as den- drimers. Dendrimers have sizes in nanometer range and can very easily be prepared and functionalized. Also, den- drimers demonstrate the ability to show numerous copies of surface groups for the process of recognition biologi- cally. Hence, they are a very attractive method for drug delivery.

Liposomes as drug particle carrier in ocular delivery-

Liposomes are basically artificial vesicles or colloidal par-ticles, which are made up of natural and non-toxic choles-terol and phospholipids as the chief constituents for developing enclosed bilayers of lipid, or lipid–drug com- plex, or a sheet–drug complex. Figure 1 shows a labeled diagram of a liposome. The liposomes are very promising for the delivery of drugs because they are biocompatible, have a very small size, and bear amphiphilic properties. The liposomes that are approved for use in humans contain neutrally charged phosphatidylcholine with fatty acyl chain of variable degree of saturation as well as different lengths. The properties shown by liposomes vary signifi- cantly with changes in the composition of lipid, its surface charge, the method that is used for

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its preparation and its size. For modulating the rigidity of the membrane, and also for reducing the instability caused due to serum–pro- tein binding with the liposomal membrane, cholesterol is included in the formulation most of the time.

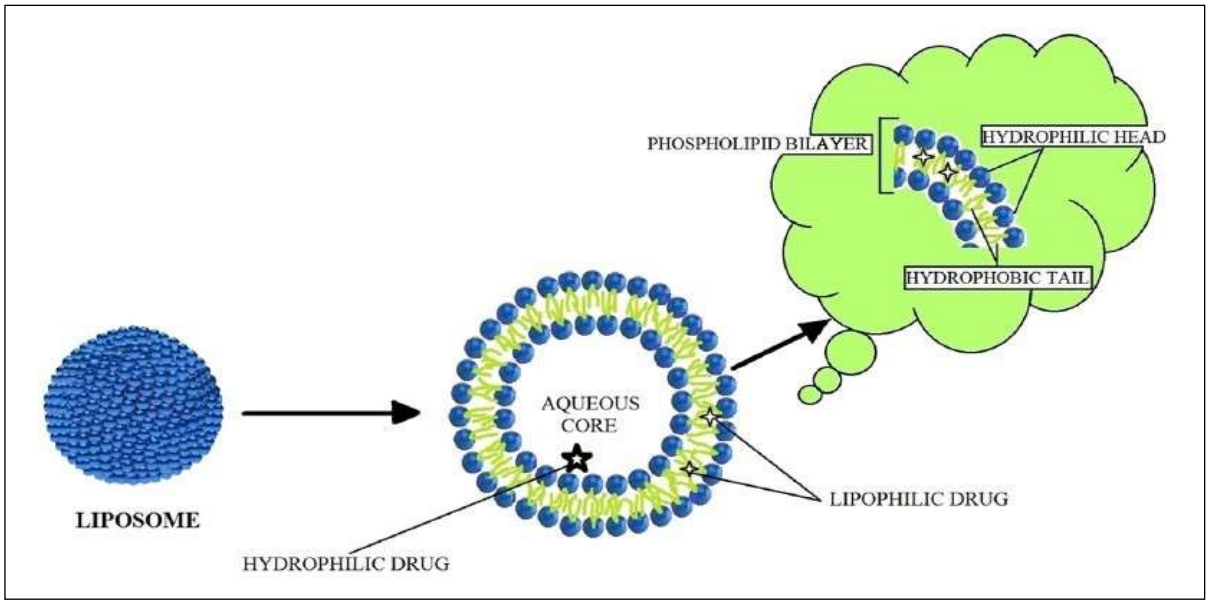

Figure 1. Labeled diagram of a liposome.

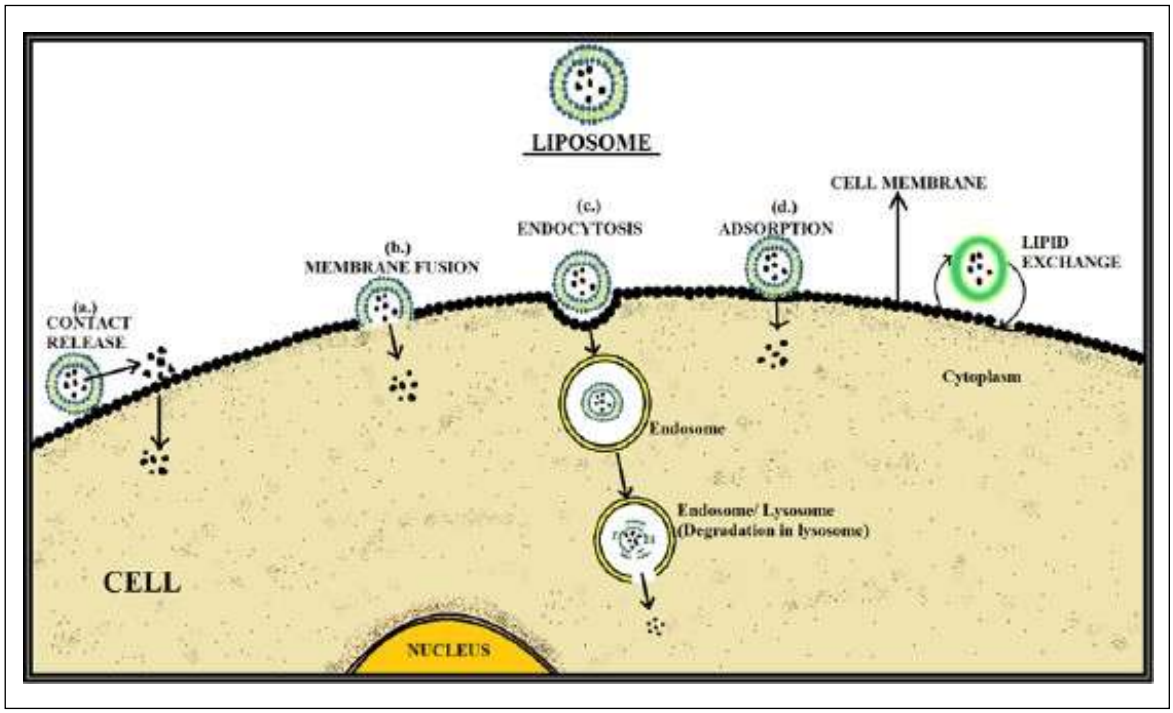

Figure 2. Schematic presentation of various drug releasemechanism from liposomes.

Mechanism of liposome–cell interaction anddrug release

Figure 2 shows a pictorial representation of how the liposomes come into contact with the cell and the various mechanisms of release of the therapeutic agents from its phospholipid bilayer. surface charge of the liposomes, whether positive, nega- tive, or neutral. It has been seen that the liposomes that bear a positive charge on their

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surface are favorably cap- tured by the negatively charged corneal tissues in compari- son with the negatively charged liposomes and the neutral ones. Furthermore, the density of these charges and their nature influences the characteristics of the formulation, such as its stability, kinetics, distribution in the body, and also determines how the target cells will interact with the liposomes.

The potential of liposomes, for carrying ACV to eye was studied by Law et al. At pH 8.0, the positively charged liposomes showed an optimum loading compared to the negatively charged ones, whereas the neutral liposomes showed intermediate loading. Particle size was optimum. In the release study, ACV released faster from the posi- tively charged liposomes at pH 7.4 than at pH 8.0. Mobility of negative and neutral liposomes loaded with ACV did not show any change, when compared to blank liposomes. However, positively charged liposomes showed a decreasein mobility.

Table 1. Few examples of ocular liposomal products.

Se. No.	Brand name	Therapeutic ingredient	Indication	Manufacturer
1.	Visudyne®	Verteporfin (photosensitizer)	Photodynamic therapy for subfoveal choroidal neovascularizatio n in age-related macular degeneration, presumed ocular histoplasmosis pathological myopia	QLT Ophthalmics, Inc., Menlo Park, CA, USA
2.	Tears Again®	Phospholipid	Dry eye syndrome	Optima Pharmaceutical GmbH, Germany
3.	Photrex®	Rostaporfin	Photosensitizing agent with the aim to treat age-related macular degeneration (currently FDA approval pending)	Miravant Medical Technologies, Goleta, CA, USA.
4.	Ciloxan®			Alcon

The liposomes that are loaded with drugs interact with the cell and release the therapeutic agents contained withinit by the following mechanisms:

Following administration, the liposomes on coming into contact with the cell may release its content onto the cell surface, which then enters the cyto- plasm of the cell.

Liposomes that are loaded with drug may also get adsorbed onto the surface of the cell either specifi- cally or non-specifically and release its content, after being destabilized by certain components of the cell membrane, and then enter the cell by the process of micropinocytosis.

Liposomes may also fuse with the membrane of the cell and deliver the therapeutic agent into the cytoplasm.

The drug-loaded liposomes may also get endocytosed either directly or indirectly, thereby being delivered into the lysosome by the endosome, and releasing the drug into the cytoplasm, following provocation of destabilization of the endosome by the liposome.

The liposomes also have the capability to undergo an exchange of its lipids with the lipids of the cel- lular membrane via the transfer-protein-mediated exchange.

Commercially available novel formulations

Here, a few examples of liposomal

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formulations for the ocu- lar space are enlisted, that are commercially available, and examples of ocular formulations that are already marketed, or under clinical trials in Tables 2 and 3, respectively:

Future aspects

Delivery of drugs to the eye, since decades, has always remained a difficult task due to the problems associated with bioavailability. Dedicated researches in the area of ocular drug delivery have led to the development of novel drug delivery systems for delivery of drugs to the eye, which have set a new standard in the efficient prevention and treatment of ocular diseases. Many researches are still being conducted so that the existing dosage forms can fur- ther be improved, bioavailability problems may be over- come, and the novel formulations show a prolonged retention in the eye and exhibit an improved release pro- file. However, the need of the hour is to develop a formula- tion, which not only targets the eye as a whole with improved characteristics but should also have the novelty of being site-specific within the eye so that treatments for both the anterior and posterior segments can be given properly. It should also be taken care of, that in the process of developing newer technologies for ocular drug delivery; the technology should be such that it is compatible with patients too. The designed formulation should be such that it contains an optimum amount of the therapeutic agent so that a single administration for treatment is adequate. There can be a speedy development in the field of ocular delivery of drugs only if the researchers are well acquainted with the proper anatomy and physiology of the eye in nor- mal as well as in diseased state, the nature of all the barri- ers within it, and the kinetics of the various compartments within the eye. This trend of newer innovations in the form of novel drug delivery system is accelerating the patient compliance level into a higher mark.

Table 2. Few examples of novel ocular formulations (marketed or under clinical trials).

S. no.	Novel ocular drug delivery system	Marketed product	Under clinical trial
1.	Emulsion	Restasis™, AzaSite®, Endura®, Durezol™, Cationorm®, Novasorb®, Restasis®, Cyclokat®, Catioprost®	Cyclosporine (NOVA22007), under phase II for dry eye syndrome, and under phase II, III for vernal keratoconjunctivitis
2.	Suspension	TobraDex®, TobraDex ST®,Maxidex®	Rebamipide (OPC-12759), under phase II
3.	Implants	Vitrasert®, Retisert®, Ozurdex®, NOVADUR®, Iluvien®,	Surodex™, Medidur®, Posurdex®, under phase III NT501, under phase II Cyclosporine (LX201) in phase III, triamcinolone acetonide, under phase I
4.	Non-viral delivery system for gene-based drugs	Vitravene®, Macugen®	siRNA molecules Bevasiranib and Sirna-027 have entered clinical trials. Pegaptanib sodium, currently under phase II trials for treatment of diabetic maculae edema
5.	Cell encapsulation		ECT product NT501, entered phaseII trials
6.	Iontophoresis	OcuPhor®, Eyegate II Delivery System®, Visulex®, OcuPhor™, Visulex™, Macroesis™	
7.	In situ gelling system	Timoptic-XE®, Pilogel®, AzaSite®, Pluronic®, Carbopol®, TIMOPTIC-XE®, Gelrite®, Durezol™, Rysmon®	

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 914-926 www.ijprajournal.com ISSN: 2456-4494

8.	Hydrogel	Eligard®, Gel-Larmes®,Fucithalmic®	
9.	Use of cyclodextrin excipient	Voltaren Ophthalmic®, Indocid®	
10.	Nanoparticulate drug inophthalmic solution	Ocusolin™	
11.	Soft contact lens		Ketotifen drug, in phase III
12.	Inserts	Ocusert®, Lacrisert®, Ocufit SR®	Latanoprost, in phase I

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