A NEW TREND: OCULAR DRUG DELIVERY SYSTEM

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ABSTRACT
Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical companies in the market. In ophthalmic formulation to the eye like solutions, suspensions, and ointments are available in the market shows drawbacks such as increased precorneal elimination, high variability in efficiency, and blurred vision. The major problem associated with the conventional dosage forms is the bioavailability of drug. In the last three decades to improve the bioavailability by common to adding viscosity-enhancing agents or mucoadhesive polymers into dosage formulations. To overcome to conventional dosage formulations there were non-conventional technologies such as nanotechnology, microspheres, microemulsion and ocular inserts could be developed in pharmaceutical market. This review focuses on recent development in conventional and non-conventional ophthalmic dosage formulation and products used to achieve prolonged contact time of drugs with the cornea and increase their bioavailability.

Keywords: Eye, ophthalmic formulations, polymers, sustained release, nanotechnology.

INTRODUCTION
Topical application of drugs to the eye is the well established route of administration for the treatment of various eye diseases like dryness, conjunctiva, eye flu etc. The protective mechanisms of the eye such as Blinking, baseline and reflex lachrymation, and drainage decrease the bioavailability of drug and also help to remove rapidly foreign substances like the dust particles bacteria, including drugs, from the surface of the eye [1].

There are many eye deceases which can be affected to the eye and also eye vision. Therefore marketed ophthalmic dosage formulations are classified as conventional and non-conventional (newer) drug delivery systems. There are most commonly available ophthalmic preparations such as drops and ointments about 70% of the eye dosage formulations in market. But these preparations when instilled into eye they are rapidly
drained away from the ocular surface due to blinking, tear flow and lacrimal nasal drainage of the eye. Only a small amount of drug is available for its therapeutic effect resulting in frequent dosing application to the eye. So overcome to these problems newer pharmaceutical ophthalmic formulation such as in-situ gel, nanoparticle, liposome, nanosuspension, microemulsion, intophoresis and ocular inserts have been developed in last three decades increase the bioavailability of the drug as a sustained and controlled manner \[2-9\].

**Anatomy and function of the eye**

The eye is a spherical structure with a wall made up of three layers; the outer part sclera, the middle parts choroid layer, Ciliary body and iris and the inner section nervous tissue layer retina. The sclera is tough fibrous coating that protecting the inner tissues of eye which is white except for the transparent area at the front, and the cornea allows light to enter to the eye.

The choroid layer, situated situated in the sclera, contains many blood vessels that modified at front of the eye as pigmented iris the coloured part of the eye (blue, green, brown, hazel, or grey) \[10\].

**The structure of the cornea**

The clear transparent bulge cornea situated at the front of the eye that conveys images to the back of the nervous system. The adult cornea has a radius of approximately 7-8mm that covers about one-sixth of the total surface area of the eye ball that is a vascular tissue to which provides nutrient and oxygen are supplied via lachrymal fluid and aqueous humour as well as from blood vessels of the junction between the cornea and sclera in fig.1 \[11\].
Figure 1
The structure of the eye

The cornea is made of five layers as epithelium, bowman’s layer, stroma, descemet’s membrane and endothelium that is main pathway of the drug permeation to eye[12, 13]. The epithelium made up of 5 to 6 layers of cells. The corneal thickness is 0.5–0.7 mm in the central region. The main barrier of drug absorption into the eye is the corneal epithelium, in comparison to many other epithelial tissues (intestinal, nasal, bronchial, and tracheal) that is relatively impermeable[12].

The epithelium is squamous stratified, (5-6 layer of cells) with thickness of around 50-100 µm and turnover of about one cell layer every day. The basal cells are packed with a tight junction, to forming not only an effective barrier to dust particle and most microorganisms, and also for drug absorption. The transcellular or paracellular pathway is the main pathway to penetrate drug across the corneal epithelium. the lipophilic drugs choose the transcellular route whereas the hydrophilic one chooses paracellular pathway for penetration (passive or altered diffusion through intercellular spaces of the cells). The Bowman’s membrane is an acellular homogeneous sheet with 8-14µm thick situated between the basement membrane of the epithelium and the stroma.

The stroma, or substania propria, composed of around 90% of the corneal thickness that contains about 85% water and about 200-250 collagenous lamellae.
lamellae provide physical strength while permitting optical transparency of the membrane. The hydrophilic solutes diffuse through the stroma’s open structure.

The descemet’s membrane is secreted by the endothelium and lies between the stroma and the endothelium\textsuperscript{[10, 11]}.  

**Conjunctiva**

The conjunctiva protects the eye and also involved in the formation and maintenance of the precorneal tear film. The conjunctiva is a thin transparent membrane lies in the inner surface of the eyelids and that is reflected onto the globe. The conjunctiva is made of an epithelium, a highly vascularised substantia propria, and a submucosa. The bulbar epithelium contains 5 to 7 cell layers. The structure resembles a pallisade and not a pavement corneal epithelium cells are connected by tight junctions, which render the conjunctiva relatively impermeable. The molecules up to 20,000 Da can cross the conjunctiva, while the cornea is restrict to molecules larger than 5000 Da. The human conjunctiva is about 2 and 30 times more absorption of drugs than the cornea and also proposed that loss of drug by this route is a major path for drug clearance.

The highest density of conjunctiva is due the presence of 1.5 million goblet cell varying with age depended among the intersubjects variability and age. The vernal conjunctivitis and atopic kerato conjunctivitis occurs due to the great variation in goblet cell density results only in a small difference in tear mucin concentration\textsuperscript{[12,13]}.  

**Nasolachrymal drainage system**

Nasolachrymal drainage system consists of three parts; the secretory system, the distributive system and the excretory system. The secretory portion is composed of the lacrimal gland that secreted tears are spread over the ocular surface by the eyelids during blinking. The secretory system is stimulated by blinking and temperature change due to the tear evaporation and reflux secretors that have an efferent parasympathetic nerve supply and secrete in response to physical and emotional state e.g. crying.

The distributive system consists of the eyelids and the tear meniscus around the lid edges of the open eye, which spread tears over the ocular surface by blinking, thus preventing dry areas from developing.

The excretory part of the Nasolachrymal drainage system consists of the lacrimal puncta, the superior, inferior and common canaliculi; the lacrimal sac, and
the nasolachrymal duct. In humans, the two puncta are the openings of the lachrymal canaliculi and are situated on an elevated area known as the lachrymal papilla. It is thought that tears are largely absorbed by the mucous membrane that lines the ducts and the lachrymal sac; only a small amount reaches the nasal passage\cite{10,13}.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{nasolachrymation.png}
\caption{Schematic diagram of nasolachrymation drainage system}
\end{figure}

**Tear film**

A thin fluid layer is covered the exposed part of the eye called as precorneal tear film. The film thickness is about 3–10 Åm depending on the measurement method with the resident volume approximately 10 µl. The osmolality of the tear fluid is approx. 310–350 mOsm/kg in normal eyes and is maintained by the monovalent and divalent inorganic ions present in fluid such as Na\(^+\), K\(^+\), Cl\(^-\), HCO\(_3\)\(^-\), and proteins. The mean pH of normal tears is about 7.4. Diurnal patterns of pH changes the pH of tear, which a general shift from acid to alkaline during the day. The buffer capacity of the tears fluid is determined by bicarbonate ions, proteins, and mucins\cite{15,16}. Tears exhibit a non-Newtonian rheological behaviour with viscosity is about 3 mPas\cite{12}. The mean surface tension of tear film value is about 44 mN/m\cite{16}.

**Ocular absorption of drug**

The common method of ocular drug delivery is topical administration of ophthalmic dosage formulation drops into the lower cul-de-sac. Such drops are outflow quickly due to the eye blinking reflux, and the precorneal region returns to maintain
resident volume of around 7µl. The available concentration of drug in precorneal fluid provides the driving force for passive transport of drug across the cornea. However, the epithelium is the predominant rate limiting barrier for hydrophilic drugs and where as stroma is rate limiting step for most of the lipophilic drugs. Recent studies suggest that the noncorneal routes of absorption are an across the sclera and conjunctiva have significant role for drug molecules with poor corneal permeability. Studies with inulin, timolol maleate, gentamicin, anesthetic and autonomic drug and PGF$_{2\alpha}$, PGF$_{2\alpha}$-1-methyl ester, and PGF$_{2\alpha}$-1-isopropyl ester suggest that these drugs gain access through the non-corneal route\textsuperscript{[17-21]}.

Thus the topically application of formulation to the surface of ocular are an extremely complicated issue because of the numerous protective mechanisms of the eye that protects the visual pathway from foreign materials. Design of modern ocular drug delivery systems is based on the drug application pathways and absorption mechanism in the eye and the overall ocular pharmacokinetic/pharmacodynamic profile. Thus for efficient drug absorption require more prolonged contact time of dosage formulation to within the eye.

**Conventional ocular drug delivery system:-**

The conventional ophthalmic drug delivery systems are used in today’s ocular disease treatment and preventions are solutions, suspensions, ointments and Bioadhesive polymer gel. In spite of significant criticisms over the efficacy and efficiency of these conventional systems, such as limitation are such as bioavailability, sterility, dosing administration. So these preparations are extensively used in a majority of commercial products in pharmaceuticals market.

**Aqueous solutions**

Today most of the topical ophthalmic preparations are in the form of aqueous solutions. A sterile homogeneous solution dosage form have many advantages over the other dosage such as formulation, including the easily commercially capability produce on large scale manufacture. There are various factors that must be consider during the formulating aqueous solution includes selection of appropriate salt of the drug, solubility in solvents, therapeutic systemic effect, ocular toxicology, pKa of formulation, and the effect of pH of the formulation. Others stability parameters includes such as solubility,
tonicity, viscosity, buffering capacity, compatibility with formulation ingredients and effect of packaging components, choice of appropriate preservative, ocular comfort and dosing administration[1].

The designing of experiments and parameters must be conducted to achieve the optimum formulation. Corneal absorption enhancement can be achieved best by increasing solution concentration and viscosity, increasing contact time of formulation in the cornea film, appropriate pKa and offering optimal lipid solubility of drug [22].

Commonly added viscosity enhancer agents to improve ocular bioavailability, these includes various synthetic polymers such as corboxymethyl cellulose, hydroxyl methylcellulose, polyvinyl alcohol, hydroxypropyl methylcellulose, and carbomers. Recently natural polymers have also been used to improve bioavailability of drugs. Examples of these polymers are hyaluronic acid (HA), guar gum, xylloglucan gum, Chitosan, gellan gum, pectin etc. The rheological characteristics of a polymer should be implicated the such as no adverse effects, contact time of dosage formulation and retention of dosage formulation ocular surface [23-24].

The solubility and stability, and corneal permeability of the drugs are depends on pH of the formulation. A factor pH of the formulation is a best possible compromise between stability and bioavailability of the drug. Ophthalmic solutions are should be formulated in between pH range 4 to 8.0. If the pH range of the formulation is outside the physiological pH range of eye, can be discomfort, irritation and also decrease the bioavailability of the drug, due to the secretion of fluid and to aid in the restoration of normal physiological conditions. The excessive tearing from the nasolacrymal gland also results into rapidly flushing of the drug. So it necessary, proper choices of buffering agents and buffer capacity are essential to optimize drug bioavailability as well as ocular efficacy of drug [25].

The typical multitasking ophthalmic product containing antimicrobial preservatives for prevention of administering microbiologically contaminated products and is to prevent the patient. The main factors to be consider for selecting a preservative for ophthalmic products are (a) a very low concentration should be effective at against a broad spectrum of microorganisms (b) it should be inert and non toxic (c) form a homogenous solution in the formulation (d) not reacts with the drug packaging
components (d) effective over the shelf life of products. The quaternary ammonium compounds have good quality of good preservatives such as e.g., benzalkonium chloride, parabens, chlorobutanol and 2-poly (ethylalcohol) and also new generation preservatives such as Purite®.

The shelf life and expiration date of the product determined by stability of ophthalmic products at various conditions. Products are analysing for physical, chemical and microbiological parameters. Physical evaluation parameters for products are pH, osmolality, viscosity, color and appearance of the product and Chemical parameters include assays (UV, IR, TLC, HPLC) for the active and degradation product and preservative/excipients content in the products[25,26].

Aqueous ophthalmic solutions are generally manufactured by a process in which the dissolution of the active and other inactive ingredients (excipients/additives) after sterilization is achieved by application of heat or by sterile filtration. This prepared sterile solution may further be then mixed with other components such as sterilized solutions of viscosity – including agents and additives. The batch is made upto final volume with additional sterile water[26].

Suspensions

Ophthalmic suspensions products is another part of the ocular drug delivery system and have many distinct advantages over others formulation. Recently developed drugs are generally hydrophobic poor solubility in water and aqueous medium. Formulation offers a sterile, preserved, effective, stable and pharmaceutically elegant. Ophthalmic suspensions are more complex and challenging if compare with to ophthalmic (aqueous) solutions.

The formulation of a ophthalmic suspension many problem occured such as non-homogeneity of the dosage form, settling of particles, cake formation, aggregation of the suspended particles. The commercial ophthalmic products of should be effectively preserved on storage. To study the surface tension properties, such as wetting, particle size and interaction zeta potential, aggregation, sedimentation rate and rheological characterization of the formulation. Above all criteria are necessary for formulating an effective, elegant suspension ophthalmic formulation[6,27].
Generally suspensions are kinetically stable at normal condition but thermodynamically unstable systems. If suspension keep undisturbed for a long duration of time, can be lead to aggregation of particles, sedimentation, settling of particles and eventually forming caking. But they are readily dispersible on hand shaking. Flocculation state of suspension the particles are held together in a loose open structure and the flocculated particles settle rapidly and for sediment. Relative properties of flocculated and deflocculated particles in suspension

**Deflocculated**

- Rate of sedimentation is slow because each particle settles separately due to the particle size is minimal.
- The sediment particle becomes very closely packed so that, a hard cake is formed due to repulsive forces between particles are overcome then is difficult to redisperse in media.
- Generally suspensions have a pleasing appearance, due to the suspended material in solution form. The supernatant also remains cloudy on settling is remains in media.

**Flocculated**

Rate of sedimentation is high because particles settle as a floc, because a collection of particles.

Particle size of the suspension has a key role in physical stability and bioavailability. The rate of sedimentation, agglomeration and resuspendability of suspensions are affected by particle size and bioavailability. In most ophthalmic suspension, the average particle size is less than 10 μm. Mostly the particle achieved by the efficient method is by dry milling and wet milling and other methods are also used of particle size reduction include micro-pulverization, grinding, and controlled precipitation [22, 26].

An ophthalmic suspension contains many inactive ingredients such as dispersing and wetting agents, suspending agents, buffers and preservatives. Wetting agents are used to decreases the contact angle between the solid surface and the wetting liquid. Generally used wetting and solubilizing agents are Benzalkonium chloride, Benzethonium chloride,
Cetylpyridinium chloride, Nonoxynol 10, Octoxynol 9, Poloxamer, Polyoxyl 50 stearate, Polyoxyl 20 cetostearyl ether, Polyoxyl 40 stearate.

Suspending agents are used to prevent sedimentation and affecting the rheological behavior of a suspension. An ideal suspending agent should have to produce a structured vehicle and it should be inert and non-toxic. Generally ophthalmic suspension used suspending agents are includes cellulosic derivatives such as methyl cellulose, cabilox methyl cellulose, and hydroxyl propyl methyl cellulose, synthetic polymers such as carbomers, poloxamers, and polyvinyl alcohol. The selection of buffers and preservatives for suspension ophthalmic solutions in almost same as aqueous except that they must also be compatible with the flocculating systems.\[^{27}\]

An ophthalmic suspension difluprednate is an active ingredient that shows superior antiinflammatory action and antiallergic action by local application for the treatment and prevention of disorders of the eye, such as conjunctivitis (allergic, vernal, blepharitis marginalis, catarrhal) and uveitis.\(^{(U.S.\,\text{patent}\,5556848)}\)[^28]. There are various ophthalmic solutions available in the market in table.1

**Gel and Bioadhesive gel**

There are many different marketed formulation adhesions depending upon the environment of the eye for prolonging effectiveness of the drug at the site of the administration (eye).

Adhesion as a process is defined as the "fixing" of two surfaces to one another.\[^{29}\]. Thus bioadhesion is the binding of a natural or synthetic polymer to a biological substrate such as a mucous layer, the term mucoadhesion is often used.\[^{30}\] Mucoadhesion has been mostly used to promote a simple way of achieving site of action drug delivery by the incorporation of mucoadhesive hydrophilic polymers within ophthalmic formulations along with the active pharmaceutical ingredient (API). The rationale behind that is the formulation will be ‘held’ on a biological surface for localised drug delivery. There are various theories: wettability theory, electronic theory, fraction theory, absorption and diffusion-interlocking theory of Bioadhesive force have been proposed in this review reference.\[^{7}\]

The API from the formulation will be released close to the site of action with a consequent increment of bioavailability.\[^{31}\]. While mucoadhesive drug delivery systems
provides a means of enhancing retention time at defined sites of application, if systemic uptake occurs the use of mucoadhesive polymers will not prove to effective distribution of the API. Chitosan (CS) a cationic polysaccharide that has widely being used in ophthalmic preparations [32]. The specific bioadhesiveness of CS to the ocular surface was first observed in an ex-vivo study, in which the activity of radiolabelled CS was measured by scintillation counting after addition to a freshly excised cornea and exhaustive rinsing 29, 32. Electrostatic attraction is the major driving force for mucoadhesion [33].

Interactions of suitable mucoadhesive natural and synthetic polymers with mucins were evaluated from biological substances. Interactions between the mucous layer and the eye tissues, an increase in the precorneal residence time of the formulation was observed. Some mucoadhesive polymers showed not only good potential to increase the bioavailability of the drug applied, but also have a protective and healing properties to epithelial cells such as Chitosan have a wound healing properties and antimicrobial properties. The Carbomer polymeric gel base itself has been used successfully to treat moderate to severe cases of dry eye such as Keratoconjunctivitis Sicca [32, 37].

Keratoconjunctivitis sicca (KCS), also called as dry eye syndrome (DES), is an eye disease caused by decreased tear production or increased tear film evaporation commonly found in humans and some animals. The choice of the polymer plays a critical role in the release kinetics of the drugs from the dosage form [38].
Table 1: There are several bioadhesive polymers now available with varying degree of mucoadhesive capacity. 

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Origin</th>
<th>Charge</th>
<th>Solubility in water</th>
<th>Mucoadhesive capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly acrylic acid (neutralized)</td>
<td>Natural</td>
<td>Anionic</td>
<td>Insoluble</td>
<td>+++</td>
</tr>
<tr>
<td>Carbomer (neutralized)</td>
<td>Synthetic</td>
<td>Anionic</td>
<td>Insoluble</td>
<td>+++</td>
</tr>
<tr>
<td>Hyaluronans</td>
<td>Natural</td>
<td>Anionic</td>
<td>Soluble</td>
<td>+++</td>
</tr>
<tr>
<td>Chitosan</td>
<td>Natural</td>
<td>Cationic</td>
<td>Soluble</td>
<td>++</td>
</tr>
<tr>
<td>Sodium CMC</td>
<td>Natural</td>
<td>Anionic</td>
<td>Soluble</td>
<td>++(+)</td>
</tr>
<tr>
<td>Poly (galacturronic) acid</td>
<td>Natural</td>
<td>Anionic</td>
<td>Insoluble</td>
<td>++</td>
</tr>
<tr>
<td>Sodium alginate</td>
<td>Natural</td>
<td>Anionic</td>
<td>Soluble</td>
<td>++(+)</td>
</tr>
<tr>
<td>Pectin</td>
<td>Natural</td>
<td>Anionic</td>
<td>Soluble</td>
<td>++(+)</td>
</tr>
<tr>
<td>PVA</td>
<td>Synthetic</td>
<td>Nonionic</td>
<td>Soluble</td>
<td>+</td>
</tr>
<tr>
<td>PVP</td>
<td>Synthetic</td>
<td>Nonionic</td>
<td>Soluble</td>
<td>+</td>
</tr>
<tr>
<td>PEG</td>
<td>Synthetic</td>
<td>Nonionic</td>
<td>Insoluble</td>
<td>+(+)</td>
</tr>
<tr>
<td>HPMC</td>
<td>Natural</td>
<td>Nonionic</td>
<td>Soluble</td>
<td>+</td>
</tr>
<tr>
<td>Poloxamer</td>
<td>Synthetic</td>
<td>Nonionic</td>
<td>Soluble</td>
<td>+(+)</td>
</tr>
<tr>
<td>Xyloglucan</td>
<td>Natural</td>
<td>Anionic</td>
<td>Soluble</td>
<td>+</td>
</tr>
<tr>
<td>Methyl cellulose</td>
<td>Natural</td>
<td>Nonionic</td>
<td>Soluble</td>
<td>+</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>Natural</td>
<td>Nonionic</td>
<td>Insoluble</td>
<td>+</td>
</tr>
</tbody>
</table>

In above table1 shows; Mucoadhesive capacity: +++: excellent; ++: good; +: poor/absent.

Nanotechnology in ocular drug delivery system

The word Nanotechnology, arise from the greek word nano meaning drawf, technology means application to the engineering, electronics, physical, material science medical and manufacturing at a molecular and a submicron level. An early promoter of nanotechnology, Albert franks, defined it as that area of science and technology where dimensions and tolerance are in the range of 0.1-100nm [40].

The nanotechnology based drug delivery system like nanosuspention, solid nanoparticle microemulsion and liposomes have developed to solve the solution of various solubility-related problem of poorly water soluble drugs, likes dexamethsone, budenoside, gancyclovir and so on [39]. Due to relative properties of the particle size charge, surface properties and relative hydrophobicity of (molecules) nanoparticles are developed to be successfully used in crossing the over-coming absorption barriers [40].
Furthermore, nanocarriers are critical in order to exploit the emerging in pharmaceutical field of drug delivery systems and new gene therapies for the treatment of ocular disorders and other alternatives for topical drug delivery involve the use of liposomes, nanospheres, nanosuspension and nanoparticles and so on.

Different nanoparticles based drug delivery systems are

**Microemulsion**

Microemulsions were first described Hoar and Schulman. Microemulsion is a dispersion of water and oil that formulated with surfactants and co-surfactants in order to stabilize the surface tension of emulsion \[^{[41]}\]. Microemulsions have a transparent appearance, with thermodynamic stability and a small droplet size in the dispersed phase (aqueous and nonaqueous phase) (<1.0µm). Microemulsion are an interesting alternative to ophthalmic formulation, due to their intrinsic properties and specific structure. They can be easily prepared through emulsification method, easily sterilized, and are more stable and have a high capacity for dissolving drugs \[^{[40, 42]}\]. The ophthalmic o/w Microemulsion could be advantageous over other formulation, because the presence of surfactants and co-surfactants increase the drug molecules permeability, thereby increasing bioavailability of drugs. Due to, these systems act as penetration enhancers to facilitate corneal drug delivery \[^{[43]}\]. The in-vivo experiments and preliminary studies on healthy volunteers have occurred a delayed effect and an increase in the bioavailability of the drug. This mechanism is based on the adsorption of the nanodroplets representing the internal phase of the microemulsions, which act as a reservoir of the drug on the cornea and should decrease their drainage in limit \[^{[43, 44]}\]. Indeed, in 2002 the FDA approved the clinical use of an anionic emulsion containing cyclosporine A 0.05% (Restasis®, Allergan) for the treatment of chronic dry eye. A similar formulation (anionic emulsion containing difluprednate 0.05%, Durezol™, Sirion Terapeutics) has recently been approved for the treatment of ocular inflammation. In the same field, a non-medicated anionic emulsion for eye lubricating purposes, in patients suffering from moderate to severe dry eye syndrome (Refresh Dry Eye Therapy®, Allergan), and two lipidic emulsions, indicated for the restoration of the lipid layer of the lacrimal fluid (Lipimix™, Tubilux Pharma, and Soothe XP® Emollient, Bausch and Lomb), have been launched in the US and European markets.the cationic nanoemulsions have also made their way onto
the market. Namely, the product Cationorm® (Novagali Pharma, France) was launched in the European market for the treatment of dry eye symptoms and two more products, based upon the same technology and intended to deliver cyclosporine A, are currently under registration or under clinical evaluation (Phase III).

Water-in-oil microemulsions (w/o ME) capable of undergoing a phase-transition to lamellar liquid crystals (LC) or bicontinuous ME upon aqueous dilution were formulated using Crodamol, sorbitan mono-laurate and polyoxyethylene 20 sorbitan mono-oleate, an alkanol or alkanediol as cosurfactant and water. The hypothesis that phase-transition of ME to LC may be induced by tears and serve to prolong precorneal retention was tested. The ocular irritation potential of components and formulations was assessed using a modified hen's egg chorioallantoic membrane test (HET-CAM) and the preocular retention of selected formulations was investigated in rabbit eye using gamma scintigraphy. Results showed that sorbitan mono-laurate, polyoxyethylene 20 sorbitan mono-oleate and Crodamol ethyl oleate were non-irritant. However, all other cosurfactants investigated were irritant and their irritation was dependent on their carbon chain length. A w/o ME formulated without cosurfactant showed a protective effect when a strong irritant (0.1 M NaOH) was used as the aqueous phase. Precorneal clearance studies revealed that the retention of colloidal and coarse dispersed systems was significantly greater than an aqueous solution with no significant difference between ME systems (containing 5% and 10% water) as well as o/w emulsion containing 85% water. Conversely, a LC system formulated without cosurfactant displayed a significantly greater retention compared to other formulations [45].

Nanoparticles

Nanoparticles are the particle with a diameter of less than 1µm, containing of various biodegradable materials, such as natural and synthetic polymer, liposomes, lipids, phospholipids and even inorganic material. Biodegradable nanoparticles of polymers like polylactides (PLAs), polycyanoacrylate, poly (d,l-lactides), natural polymers can be used effectively for efficient drug delivery to the ocular tissues.

Pre-clinical Studies by Bourges et al. in rabbits shows that nanoparticles of different size and electric charge, when injected into the vitreous, migrate through the retinal layers and tend to accumulate in the retinal pigment epithelium (RPE) cells. They
found that presence of nanoparticles within the RPE cells up to four months after a single intravitreous injection \cite{46}. The movement of nanoparticles in the internal limiting membrane (ILM) because of the modification of the vitreous interface structure secondary to the presence of the PLA and poly (d,l-lactide-co-glycolide) (PLGA) \cite{47}.

The encapsulated nanospheres may also increases when in such bioavailability of ophthalmic delivery. Recently, it reported that non-biodegradable polystyrene nanospheres observed within the neuroretina \cite{46}. Generally nanoparticles act at the cellular level and followed to endocytosed/phagocytosed by cells, then resulting cell internalization of the encapsulated drug. The surface charge and the binding of the drug to the particles were found to be more important factors in the drug loading in case of nanoparticles. Li et al. Proved, though being fully encapsulated in polybutyl cyanoacrilate nanospheres, the drug progesterone not released properly, because of strong interaction between the drug and the polymer \cite{48}.

The albumin nanoparticles was used to a very efficient ocular delivery system for like CMV retinitis, they are biodegradable, non-toxic and have non-antigenic effects. Since high content of charged amino acids, albumin nanoparticles allow the adsorption of positively charged gancyclovir or negatively charged particles like oligonucleotides that increased the bioavailability \cite{49}. However nanoparticles of natural polymers which are made up of like sodium alginate, chitosan, are very effective in intraocular penetration for some specific drugs, because of contact time with corneal and conjunctival surfaces. Studies results show the bioavailability of encapsulated indomethacin doubled when Poly(epsilon-caprolacton) (PECL) nanoparticles were coated with Chitosan \cite{50}. Greater corneal penetration enhancement was occurred, when PECL nanoparticles were coated with polyethylene glycol (PEG). All these studies lead us to believe that nanoparticles have great potential ophthalmic delivery systems for ocular tissues \cite{51}.

**Nanosuspensions**

Nanosuspension contains of pure, hydrophobic drugs (poorly water soluble), suspended in appropriate dispersion medium. Nanosuspension technology are utilised for drug components that form crystals with high energy content molecule, which renders them insoluble in either hydrophobic or hydrophilic media \cite{52}. 
Although nanosuspensions offer advantages such as more residence time in a cul-de-sac and avoidance of the high tonicity created by water-soluble drugs, their performance depends on the intrinsic solubility of the drug in lachrymal fluids after administration. Thus, the intrinsic solubility rate of the drug in lachrymal fluid controlled its release and increase ocular bioavailability. However, the intrinsic dissolution rate of the drug after application will vary because of the constant inflow and outflow of lachrymal fluids. However, a nanosuspension, by their inherent ability to improve the saturation solubility of the drug in media, also represents an ideal approach for ophthalmic delivery of hydrophobic drugs in eye. Moreover, in earlier nanoparticulate nature of the drug allows to prolonged residence (ocular surface) in the cul-de-sac, giving sustained release of the drug. To achieve sustained release of the drug, nanosuspensions can be incorporated or formulated with a suitable hydrogel or mucoadhesive base (in-situ gel) or even in ocular inserts [53].

A recently approaches been developes desired release the drug is the formulation formulated with polymeric nanosuspensions particles loaded with the drug. The bioerodible as well as water soluble/permeable polymers could be used to sustain and control the release of the medication. The nanosuspensions can be formulated by using the quasi-emulsion and solvent diffusion method [54]. The using acrylate polymers such as Eudragit RS 100 and Eudragit RL 100 in polymeric nanosuspensions of flurbiprofen and ibuprofen have been successfully formulated, and these have been characterized for drug loading, particle size, zeta potential, in-vitro drug release, ocular tolerability and in-vivo biological performance in animal [55]. The flu is a non-steroidal anti-inflammatory drug (NSAID) that using in inflammation and antagonizes papillary construction during intraocular surgery. Since the flu-loaded Nanosuspension are formulated by the quasi-emulsion solvent diffusion (QESD) method in which generally avoids using of toxic chemical. They are proved to great potential for ophthalmic application [56].

**Iontophoresis**

Iontophoretic technique is used to depth penetration of topically applied drug loaded nanoparticles Iontophoresis is a method for enhancing charged drug penetration into anterior and posterior ocular structures, by using a low electric current. The mechanisms of drug penetration are followed by iontophoresis of electropulsion,
electroosmosis and current-induced tissue damage \cite{8}. However, each drug has to be evaluated for its penetration capacity and pharmacokinetically profile, due to different physicochemical properties of the drug molecules. This novel approach of charged nanoparticles iontophoresis can benefit from: (1) deep penetration, regardless of drug's ionic activity strength and diffusion capacity in ocular tissues, (2) controlled and sustained release of the drug for better therapeutic activity, (3) targeting to a specific desired tissue and lacaalised tissues \cite{57}.

**Advantages**

- Increases the bioavailability and decreases the adverse effects.
- Iontophoresis of charged nanoparticles as drug carriers, providing a long duration therapeutic activity.
- Topical ophthalmic preparation and easy to apply.
- Good drug penetration to the anterior and posterior segments of the eye by topically.
- May combine to other drug delivery system.
- Good acceptance by the patients \cite{58, 59}.

**Ocular inserts**

The ocular insert represents a significant advancement in the therapy of eye disease. Ocular inserts are described as single, sterile, thin, and multilayered, drug-impregnated, solid or semisolid consistency devices, whose size and shape are especially designed for application in eye. A polymeric support is must for the ocular inserts which may or may not contain the drug. The drug is later entrapped or dispersed or the drug can be incorporated as a solution in the polymeric supports which have advantages as they increases the residence of the drug in the eye so a sustained release dosage form would be formulated. The body portion of the eye is sized in such a way so that it can position in to position in lachrymal canaliculus of the eyelid. We can classify the inserts on the basis of their solubility as insoluble, soluble, and bioerodible inserts. The drug release from the inserts would take place by following three procedures 1) diffusion, 2) osmosis, and 3) bioerosion \cite{60, 61}.

Ocular inserts serves as an alternative approach to overcome the problems which were faced by other ocular drug delivery systems \cite{61}. The commonly faced problems are
Disposition and elimination of a therapeutic agent depends on the physicochemical properties and relevant ocular anatomy and physiology \[^{[62]}\]. To design a successful delivery system for ophthalmic use, it is required to have a complete knowledge about the drug profile and other related constraints of the ocular route. Hornof et al., studies that inserts based on thiolated poly(acrylic acid) were not soluble and had good cohesive properties. In addition, a controlled release was achieved for the incorporated model drug sodium fluorescein. In past In vivo studies done on human volunteers concludes that inserts formulated using thiolated poly(acrylic acid) attains a fluorescein concentration on the ocular surface for more than 8 h, while the concentration of fluorescein starts decreasing rapidly after the application of aqueous eye drops or inserts based which were formulated using on unmodified poly(acrylic acid) \[^{[63]}\]. mostly inserts are well accepted by the humans. so these studies concludes that ocular inserts made using thiolated poly(acrylic acid) are positive approach towards newer solid devices for ocular drug delivery \[^{[6]}\].

**Table 2: Current marketed ophthalmic implants**

<table>
<thead>
<tr>
<th>Registered name</th>
<th>Active substances</th>
<th>Implant size</th>
<th>Marketing status</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>vitrasert®</td>
<td>Ganciclovir</td>
<td>Millimeter</td>
<td>Clinical use</td>
<td><a href="http://www.bausch.com">www.bausch.com</a></td>
</tr>
<tr>
<td>retisert®</td>
<td>Flucinolone acetonide</td>
<td>Tablet 3mmx 2mmx 5mm</td>
<td>Clinical use</td>
<td><a href="http://www.bausch.com">www.bausch.com</a></td>
</tr>
<tr>
<td>Medidur</td>
<td>Flucinolone acetonide</td>
<td>Cylindrical tube 3.5 mm in length and 0.37 mm in diameter</td>
<td>Phase 3</td>
<td><a href="http://www.psivida.com">www.psivida.com</a></td>
</tr>
<tr>
<td>Posurdex</td>
<td>Dexamethasone</td>
<td>Microsized implant</td>
<td>Phase 3</td>
<td><a href="http://www.retinalphysician.com">www.retinalphysician.com</a></td>
</tr>
<tr>
<td>Ozurdex®</td>
<td>Dexamethasone</td>
<td>Intravitreal implant 0.7 mg</td>
<td>Clinical use</td>
<td><a href="http://www.allergan.com">www.allergan.com</a></td>
</tr>
</tbody>
</table>

**Table 3: List of various ophthalmic marketed products in different formulation** \[^{[64,65,66]}\]

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Drug</th>
<th>Dosage form</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dichol</td>
<td>Carbachol</td>
<td>Sterile solution and prefilled syringes</td>
<td>in the treatment of glaucoma, also used in ophthalmic surgery.</td>
</tr>
<tr>
<td>Dilon</td>
<td>sodium hyaluronate</td>
<td>a sterile non</td>
<td>use to protect eye tissues such as</td>
</tr>
</tbody>
</table>

[www.pharmasm.com IC VALUE – 4.01](#)
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Active Ingredient</th>
<th>Formulation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>REFRESH TEARS®</td>
<td>Hydroxypropylmethylcellulose</td>
<td>Drops</td>
<td>As a eye lubricants and dryness of eye</td>
</tr>
<tr>
<td>RESTASIS®</td>
<td>Cyclosporine</td>
<td>Emulsion</td>
<td>Chronic dry eye (keratoconjunctivitis sicca)</td>
</tr>
<tr>
<td>REFRESH® Classic</td>
<td>Artificial tear fluid</td>
<td>Convenient single use vials</td>
<td>Moisturizes and relieves dry, irritated eyes</td>
</tr>
<tr>
<td>ciplox®</td>
<td>Ciprofloxacin</td>
<td>Drops</td>
<td>Eye infection and conjunctivitis</td>
</tr>
<tr>
<td>Geltex/Viscotear</td>
<td>Carbomer</td>
<td>Bioadhesive gel</td>
<td>Lubricants, treatment of the symptoms of dry eye such as soreness, burning, irritation or dryness</td>
</tr>
<tr>
<td>Botox®</td>
<td>Onabotulinumtoxin A</td>
<td>Sterile solution</td>
<td>Debilitating conditions as cervical dystonia, blepharospasm, strabismus,</td>
</tr>
<tr>
<td>Visudyne</td>
<td>Liposomal verteporfin</td>
<td>Sterile solution</td>
<td>Age-related macular degeneration, pathologic myopia, ocular histoplasmosis</td>
</tr>
<tr>
<td>Macugen</td>
<td>Polyethylene glycol and vascular endothelial growth factor aptamer</td>
<td>Sterile solution intravitreous</td>
<td>Age-related macular degeneration</td>
</tr>
<tr>
<td>Timolol® XE</td>
<td>Timolol maleate</td>
<td>In-situ gel</td>
<td>Dry eye and keratoconjunctivitis</td>
</tr>
<tr>
<td>Ketolags opth</td>
<td>Triaaminolone maleate and gramicidin</td>
<td>Ointment</td>
<td>Anti-infective,.Anti-inflammatory and antiallergics</td>
</tr>
<tr>
<td>Acivir eye</td>
<td>Acyclovir</td>
<td>Ointment</td>
<td>Anti-infective</td>
</tr>
<tr>
<td>Ocupol</td>
<td>Polymixin-B sulphate</td>
<td>Drops and ointment</td>
<td>Bacterial infection, stye, corneal ulcer, ulcerative blepharitis</td>
</tr>
<tr>
<td>PRED FORTE®</td>
<td>Prednisolone acetate</td>
<td>Suspensions</td>
<td>Antiallergic and anti-inflammatory</td>
</tr>
<tr>
<td>FML®</td>
<td>Fluorometholone 0.1%</td>
<td>Suspensions</td>
<td>Treatment of corticosteroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe.</td>
</tr>
</tbody>
</table>

**CONCLUSION**

The main efforts in ocular drug delivery during the two decades has been on the design of systems, to prolong the residence time of topically applied drugs at the ocular
surface and conjunctival sac. The development of ophthalmic drug delivery systems is easy because we can easily target the eye to treat ocular diseases as well as complicated because the eye has specific characteristics such eye protecting mechanism, which make ocular delivery systems extremely difficult. The most widely developed drug delivery system is represented by the conventional and non-conventional ophthalmic formulations to polymeric hydrogels, nanoparticle and nanosuspensions, microemulsions, iontophoresis and ocular inserts. Currently, very few new ophthalmic drug delivery systems have been commercialized in which them ocular inserts have been mostly used. In future an ideal system should be able to achieve an effective drug concentration at the target tissue for an extended period of time, while minimizing systemic exposure and the system should be both comfortable and easy to use.

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