A BRIEF REVIEW ON MEDICATED CONTACT LENSES

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ABSTRACT

Current ophthalmic drug delivery systems are insignificant as it gives low bioavailability and short time drug release, for example, eye drops, in which 95% of the drug is lost due to absorption through the conjunctiva or through the tear drainage. Drug delivery through therapeutic contact lenses increases the bioavailability of the drug by the controlled and extended-release on the surface of the eye and also enhances the mean residence time of the drug in the eye cavity. Therapeutic contact lenses can prevent infections and the unwanted reactions of eye tissues and can act as a drug reservoir for the treatment of several other ocular pathologies. The contact lens prevents the drug from being waste by releasing the drug into the tear layer, where it ultimately diffuses into the eye. This review article focuses focus on the potential of therapeutic lenses as effective dosage forms for the ophthalmic drug delivery systems.

Keyword: Ophthalmic Drug Delivery, Contact Lenses, Hydroxy Ethyl Methacrylate (HEMA), Poly Methyl Methacrylate (PMMA), Polymerisation, Hydrogels

1. INTRODUCTION

The ordinary delivery of drugs by eye drops currently accounts for more than 90% of all ophthalmic formulations which is very inefficient and in a certain case leads to serious side effects. Thus, to expand the residence time of the medication in the eye, accordingly decreasing wastage and minimizing reactions, various researchers have proposed utilizing contact lenses for ophthalmic drug conveyance. (1) The market for contact lenses is ever-growing, global market size worth $7.1 billion in 2015 and $12.79 billion in 2019 and is anticipated to expand at a 5.0% from 2020 to 2027. A search of patent literature shows that approximately 100 patents have been filed since 2000, representing the growing popularity of contact lenses. The applications of contact lenses range from corrective vision to therapeutics and also use for cosmetic appearance. Within these applications comes the demands from end-user of the lenses, including the length of wear, comfort, durability, practical of handling, the stability of vision, etc. This also means that within the applications of contact lenses comes the demands from manufacturers, such as material costs, ease of production, and reliability of the contact lenses, etc. finally, the demands from manufacturers determine the parameters of the material which scientists must focus their research on for developing contact lenses materials. (2,3) The first contact lenses were made from glass shells filled with jelly. Early contact lenses were uncomfortable and often very unhealthy for the eye. In the 1930s suitable polymers were discovered and by 1950 the first polymer contact lenses were being made Poly (methyl methacrylate) (PMMA) was the first successful polymeric contact lens (Contact lens) material introduced in the market in the 1960s. These Contact lenses are rigid, time-consuming to fit, and not very comfortable to wear. Research into new types of polymers led to the development of hydrogels, the first biomaterials designed for clinical use. They consist of a cross-linked polymeric network with a high capacity of water absorption and have been extensively used in numerous biomedical applications since the early 1960s.
A contact lens is a prescription medical device that is manufactured from a high-grade plastic polymer. These lens rests on the front surface of the eye (in the corneal surface) and works like eyeglasses - it bends light rays so that images are properly focused on the retinal surface. They are particularly attractive for ophthalmic drug delivery systems as these significantly increase the residence time (typically days) of the drug in the eye, a high degree of comfort, and enhances the drug bioavailability considerably. Commonly the labels of “hard” or “soft” are used as blanket definitions of contact lenses. Hard contact lenses are rigid, gas permeable lenses whereas therapeutic/soft contact lenses are flexible, high water contact lenses. The term “therapeutic” was derived from the Greek word “therapeuein” which means to take care of or to heal. Also, the term “therapeutic” is often applied to use for a specific type of contact lens, when in reality, nearly every lens type can be used in a therapeutic capacity. Therapeutic lenses are often used in the treatment and management of non-refractive disorders of the eye. This therapeutic contact lens helps the patient to see and protecting an injured or diseased cornea from the constant rubbing of blinking eyelids, thereby allowing it to heal efficiently. They are used in the treatment of conditions including dry eyes, corneal abrasions, erosion, keratitis, and corneal edema, etc. Several approaches have been used to incorporate drugs into contact lenses like “loading drugs into preformed lenses(soaking method)”, “manufacturing the lens with the drugs entrapped inside”, “dissolving the drug in the monomer solution and followed polymerization(molecular imprinting)”, “nanoparticles encapsulated contact lens(colloidal nanoparticle laden therapeutic contact lens)”, “ion exchange reaction with hydrogel functional groups(chemical functionalization)”; drug delivery with vitamin E diffusion barriers, and supercritical fluid technology.

PMMA is an optically clear (transparent) thermoplastic, high impact strength, lightweight, shatter-resistant polymer with hydrophilic character. However, PMMA has very low oxygen permeability, which may lead to several eye health issues. The researchers quickly discovered polymer hydrogels by using HEMA and develop the soft contact lenses which are composed of hydrophilic monomers, meaning they obtained electrochemical polarity allowing interaction with water. These hydrogels were biocompatible, oxygen-permeable, and flexible class of material that could hold a large percentage of water within the polymer network. These factors improved the comfort, oxygen permeability, wear time, and handling of contact lenses. The next evolution of contact lenses was silicone-based rigid lenses and hydrogels. It became the first choice of wearers which was 67% in 2016 but silicone materials are inherently hydrophobic, which means they affect the eye. Then researchers overcame this by using copolymerization of a silicone monomer with hydrophilic comonomers (Poly (Hydroxyethyl methacrylate) or PHEMA) to add the desired hydrophilic character. The water content of these lenses is around 40% and doesn’t cause dryness in the eyes. Then the next process uses longer backbone polymer chains that result in less cross-linking and increased wetting without surface alterations. This lens is more flexible and greater water content than other lenses. The entrapment of drugs in this vehicle makes additional partitions, the diffusion of drugs is considerably impeded and the drug release from these vehicles.
in therapeutic contact lenses can be sustained for a long period. This concept of additional portioning in therapeutic contact lenses has proven its usefulness by mathematical models based on the numerically calculated solutions of Fick’s laws of diffusion, and the resistance to mass transport at the interface between drug-loaded vehicles and the matrix of contact lenses has been found to be an important factor in sustained drug release.

**Figure 2: - Drug release from contact lenses**

2. SELECTION OF CONTACT LENS MATERIAL

Contact lenses range from hard to soft. Hard lenses are mainly made up of the polymethyl methacrylate (PMMA) and are impermeable to oxygen. Hard and semirigid lenses are made up of copolymers of siloxanes and methacrylates and permeable for oxygen. Flexible, oxygen permeable lenses are made of silicones. Soft lenses are prepared from polymers that absorb large quantities of water to become hydrogels. Contact lens material should be selected on the basis of their oxygen permeability, mechanical properties, water content, wettability, and lens thickness. Lens thickness affects oxygen permeability. The overall lens thickness profile is also important along with central, mid-peripheral, and edge thickness. Local thickness is the only relevant thickness when calculating local oxygen availability since there is little tear mixing under a soft lens. Thin lenses are mostly preferred because Oxygen permeability is high in thin lenses (below 0.10mm) and low in thick lenses. Water content is also needed for the contact lens. Water content improves the oxygen permeability. Low water content (20-40%), medium water content (41-60%), high water content (> 60%), oxygen is more permeable in high water content.

**Figure 3: - Relation between oxygen permeability, lens thickness and water content**
**oxygen permeability** is more important for the selection of material for contact lens preparation. This describes how much oxygen can be delivered through a contact lens. Oxygen needs to be delivered to the corneal surface to avoid eye health issues. Oxygen permeability is the most important parameter for soft contact lenses. The oxygen permeability of contact lens material is commonly measured in two ways: DK AND Equivalent oxygen percentage (EOP). Dk is the industry standard for the measurement of contact lens oxygen permeability. Where D represents diffusion and k represents solubility. Higher the Dk, the more permeable the material. The total oxygen permeability of the lens is finding out by Dk/t or Dk/L, where t or L represents the thickness. When the lens is thicker, the oxygen permeability is reduced. When the lens is thinner, the permeability is increased. The Boundary layer effect reduces the effective Dk/t of a contact lens while it is on the eye. A boundary layer is formed when oxygen molecules arrive at the front surface of the lens faster than they can penetrate. At the back surface of the lens, depending on the interfacing surfaces, a boundary layer can form if the oxygen arrives faster than it can be carried away. This overcrowding forms the boundary layers that entrap oxygen at the interfacing surfaces. The interface with fluid on the front or back surface of the lens slows down the transmission of oxygen so it should be necessary to reduce the boundary layer effect. EOP is a clinical measurement that quantifies oxygen permeability. EOP measures the amount of oxygen delivered to the cornea while the total barrier effect of the lens in the eye is taken into account. Mechanical properties are related to rigidity, stability, and flexibility. Rigidity and stability are needed to make the lens rigid and provide high-quality optics. The addition of various monomers can change the surface characteristics, thereby making the material more scratch resistant. Material toughness is measured simply by flexing the lens material until it breaks. Flexibility is needed for soft contact lenses. According to Tranoudis and Efron, surface scratch resistance (hardness) is inversely proportional to the Dk. Wettability is an important characteristic of lenses because of the hydrophobicity of many polymers. A lens must have a surface that wets well and attracts a smooth tear film. Wetting angles indicate a polymer’s affinity for water. The lower the angle, the better the wettability. Sessile drop, captive bubble, and Wilhelmy plate are different in vitro methods for measuring wetting angle.

**3.CONTACT LENS MATERIAL FOR SOFT LENSES**

Hydrogel-based contact lenses have several advantages over the hard and oxygen-permeable lenses. These lenses are less irritating, convenient to fit, can be worn for a longer time, etc. the use of synthetic hydrogels based on hydroxyethyl methacrylate (HEMA) for medical applications in 1960. **HEMA-based hydrogels** were the original and still most commonly used hydrogels for contact lenses. (11). This monomer, which is commercially available, is prepared in a single step from methyl methacrylate or methacrylic acid. This hydrogel can be prepared by the polymerization of HEMA. HEMA can be polymerized by radical initiators or by various methods (y-rays, UV, and plasma). When the monomer is purified (without EGDMA, which is a crosslinking product), a soluble polymer can be synthesized, but when the monomer contains even a low percentage of EGDMA (ethylene glycol dimethacrylate), the prepared copolymers produce swollen gels in water and in many other solvents. Syndiotactic PHEMA is synthesized at -400 C temperature by using UV catalysis and isotactic PHEMA is prepared through hydrolysis of poly benzoxoxyethyl methacrylate (PBMC) which was also synthesized from the polymers of dibutyl lithium cuprate as a catalyst. (12) HEMA highly polar properties, mean these contact lenses have generally suitable wetting properties, meaning they are comfortable. The oxygen permeability of these gels is suitable for longer wear, but silicone-based lenses are best from these lenses due to their more flexibility and more oxygen permeability.

**3.1. Polymerization technique**

Several polymerization techniques have been used to synthesize and prepare HEMA hydrogels and other polymer hydrogels such as solution polymerization or aqueous polymer solution, radiation polymerization or photopolymerization, suspension polymerization, reversible addition-fragmentation chain transfer polymerization, and also from free radical polymerization. In these techniques, the products of PHG can be formed or reformed into small particles, powder, fibres, membranes, microbeads, and even liquids by using some other substantial machines. Therefore,
these three techniques are the main focus next. In the Solution Polymerization of the, ionic or neutral monomers are mixed with the multifunctional cross-linking agent. The polymerization is initiated thermally by UV-irradiation or by a redox initiator system. The presence of solvent is the major advantage of the solution polymerization over the bulk polymerization method to serve as a heat sink. The prepared PHGs have to be washed with distilled water to remove unreacted monomers, oligomers, cross-linking agents, initiators, soluble and extractable polymers, and other impurities. Phase separation occurs and the heterogeneous PHGs are formed when the amount of water during polymerization is more than the water content corresponding to the equilibrium swelling. This method has been used to prepare varieties of PHGs in the last decades. Suspension polymerization is one of the successful methods used to prepare spherical PHGs or micro-particles with a size range of 1 mm to 1 mm. In suspension polymerization, the monomer solution is dispersed in the non-solvent, forming fine monomer droplets, which are stabilized by the addition of stabilizer. The polymerization is initiated by radicals from the thermal decomposition of an initiator. The newly formed micro-particles are then washed to remove unreacted monomers, cross-linking agent, and initiator. The shape of particles produced can be affected by the viscosity of the monomer phase, while the size of particles can be controlled by the hydrophilic-lipophilic balance (HLB) of each type of suspending agent. Some PHGs micro-particles of poly (hydroxyethyl methacrylate) have been prepared by this method. Also, the technique of inverse suspension is used for preparing PHGs of polyacrylamide because it easily removes and manages the hazardous residual acrylamide monomer from the polymer.

Figure 4: Solution And suspension polymerization

3.2. Irradiation Polymerization

In this polymerization ionizing high energy radiation, such as gamma rays and electron beams, has been used to initiate the polymerization for preparing the PHGs of unsaturated compounds. The radiolysis of water molecules results in the formation of hydroxyl radicals, which also attack the polymer chains resulting in the formation of macro-radicals. The recombination of the macro-radicals on different chains leads to the forming of covalent bonds and finally a cross-linked structure. Examples of polymers cross-linked by this method are poly (vinyl alcohol), poly (ethylene glycol), and poly (acrylic acid). The major advantage of the radiation initiation over the chemical initiation is that the production relatively pure and initiator-free. (13) Free radical polymerization is used for the preparation of HEMA hydrogels. This method usually involves polymerization by which a polymer forms by the successive addition of free radical building blocks and these free radicals can be formed by different methods, which usually involve the separation of initiator molecules. Following its generation, the initiating free radical adds (nonradicals) monomer units, thereby growing the polymer chain. The free-radical
polymerization process is consisting of 3 steps (initiation, propagation, termination, and chain transfer). Initiation is the first step of free radical polymerization and it is initiated by thermal decomposition, photolysis, redox reactions, and electrolysis of monomer and then propagated. After a radical initiator is formed, it attacks a monomer and increases the chain. Chain termination is indefeasible in radical polymerization due to the high reactivity of radicals. Termination can occur by several different mechanisms (a combination of two active chain ends, radical dispropagation. Reverse addition-fragmentation chain transfer polymerization is also an important polymerization technique. Initiation, chain propagation, and chain termination in RAFT polymerization are somewhat alike to those in conventional radical polymerization. However, the most basic and important step for the RAFT process, radical reversible addition-fragmentation equilibrium. In a RAFT process, the radical initiator reacts with the monomer to give propagating radicals. Subsequently, propagating radical adds to the c=s group originated from the RAFT agent (chain transfer agent, CTA) and intermediate radical will be generated.

Interestingly, the appearance of intermediate radical will restrict the irreversible termination reaction between the propagating and intermediate radical will also give two types of fragmentation benefited from the activity of c=s group.it is possible to return to their initial state to get a propagating radical and RAFT agent, while the intermediate radical may fragment into new radical and a dormant chain (polymeric thiocarbonylthio compound). Then, new propagating radicals will be formed after the re-initiation monomer polymerization by the new formative radicals. In this case, a rapid equilibrium will be formed between the dormant species and active propagating radicals, which enable all of the chains to Have an equal chance to grow, leading to a similar degree of polymerization. The termination reaction often is inevitable in a radical polymerization system. For RAFT polymerization, the termination reaction could be minimized, due to the existence of thiocarbonylthio end-grouping resulting in polymeric chains, which also enables participating in RAFT polymerization as a RAFT agent. Novel RAFT techniques involve the photoinitiation, redox initiation, metal catalytic initiation, enzyme initiation, acid initiation and other include SET-RAFT polymerization.

![Diagram](image)

**Figure 5: - Free radical and RAFT polymerization**

### 3.3. Silicone based lenses

These are the most common types of lenses today due to their highest oxygen permeability. This includes silicone, siloxanes, fluoro siloxanes, and other derivatives. These lenses are durable, originating from the high Si-O bonding energy, often with a higher modulus than conventional polymer hydrogels. This applies to rigid contact lenses, as the modern silicone hydrogel has a similar modulus to HEMA-derived hydrogels. The high modulus is related to causing irritation to the eye, such as the conjunctiva of the inner eyelid. In fact, the discomfort and dryness of silicone-based lenses are two of the main reasons for the user’s discontinuation. Specifically, the wettability of the lens and the incompatibility with the cornea environment in vivo requires detailed study to
improve these parameters. This includes using many combinations of comonomers with silicone monomers. Then silicone monomers are subjected to post-fabrication processes such as plasma treatment, to improve lens wettability. These techniques are most effective. The bioavailability of silicone hydrogel was independent of the plasma treatment. To improve bioavailability, new chemical modification techniques, with or without plasma treatment, are becoming of interest. Chitosan is a naturally derived polymer (from chitin) with high bioavailability originating from the hydroxyl and amine groups within the structure, lending itself to lens modification. They improve the bioavailability of plasma-treated silicone hydrogels. Polyvinyl alcohol hydrogels are contact lenses, which contain polyvinyl alcohol have excellent hydrophilic and biocompatible properties. PVA Hydrogels were of attention to several researchers in the early 1990s. These are also undergoing several chemical modification techniques to improve the bioavailability. The PVA Hydrogels are better than HEMA and silicone hydrogels such as low cost, high bioavailability, and wettability properties. NHS-PEG-biotin hydrogel contain the NHS-PEG-biotin molecules being bonded onto the surface amine bunches via carbodimide science. Neutravidin was then introduced onto PEG-biotin layer, and then liposomes that contain PEG-biotinylated lipids were docked onto the surface-immobilized neutravidin with a continuous expansion of further neutravidin and liposome layers empowered the creation of multilayers. These multilayers minimizing the danger of liposome separating from contact lens surfaces but decrease the oxygen permeability so it is not suitable. Hyaluronic acid modified hydrogels contain hyaluronic acid which is a hygroscopic biopolymer that naturally occurs within the human body. This is an important material for a wide range of tissue engineering purposes. From the chemical structure, we can see why it is useful for incorporating into CL materials. The amino acid and hydroxyls groups present in each repeating unit provide the necessary hydrophilic character, leading to high biocompatibility. The incorporation of HA was shown not to affect the surface morphology of the contact lens even after 12h of wear, showing the stability of modification of these modifications. HA is typically a graft/encapsulating to other established contact lens hydrogels. HA is an increasingly popular material for the modification of both HEMA-hydrogel and silicone-hydrogel contact lenses.

4. METHODOLOGY TO DESIGN THERAPEUTIC CONTACT LENSES

4.1. Soaking method

It is the simplest, cost-effective, and easiest way to load drugs into the contact lenses, which involves soaking of the preformed contact lenses in the drug solution by drug uptake and release mechanism in pre- and post-lens tear film. Contact lenses have the ability to receive/accommodating the drug molecules from internal channels/cavity. Their drug reservoir ability strongly depends on the water content, the thickness of lenses, the molecular weight of the drug, soaking time period, and concentration of the drug in the soaking solution (Xinning et al., 2008). As an alternative, one can also insert contact lenses into the eyes and then apply eye drops. By this method, a drug can be absorbed and released by the contact lens into the cavity and provides therapeutic action (Schrader et al., 2006).

4.2. Molecular imprinting

Molecular imprinting (MI) is one of the advanced methodologies explored by Alvarez-Lorenzo and co-workers using hydrogel contact lenses for high drug loading and controlled drug delivery (Andrade Vivero et al., 2007). This technique involves the mixing of target drugs with functional monomers, which rearranges and interacts with drug molecules. After polymerization, the drug from the contact lens is removed, which results in the formation of tailored active sites or imprinted pockets called macromolecular memory sites, i.e. the 3D structure of the drug is left behind within a flexible macromolecular network. The monomers in the hydrogel matrix are organized in such a way that high drug affinity molecular sites are created. These molecularly imprinted sites mimic the drug’s receptors or its structurally similar analogy, which increase drug loading capacity (Alvarez Lorenzo et al., 2002; Hiratani et al., 2005b; White & Byrne, 2010). The type of functional monomers used as well as their ratio in the polymeric matrix governs the drug affinity and its release profile. Thus, one can tailor the release pattern based on monomer composition.

4.3. Colloidal nanoparticles laden therapeutic contact lens
The technique is based on the ability of colloidal nanoparticles (polymeric nanoparticles, liposomes, niosomes, microemulsion, micelles, etc.) to entrap or encapsulate drug and control its release rate from contact lenses (Gupta & Chauhan, 2010; Jung et al., 2013; Hsu et al., 2014). Such formulated nanoparticulate system &#40;10 to 100 nm#41; is dispersed in HEMA monomers and polymerized using ethylene glycol-dimethacrylate (EGDMA) and photo initiator (Darocur) to fabricate therapeutic contact lenses (Gulsen & Chauhan, 2004; Bazzaz et al., 2014). Drug laden nanoparticles prevent the interaction of the drug with polymerization mixture and also offer additional resistance to drug release. Thus, the nanoparticles loaded contact lenses can deliver drugs at a controlled rate for an extended period of time. Drug loaded nanoparticles or globules (microemulsion) also bypass, to some extent, drug metabolism from the enzymes like lysosomes, present in the tear/corneal epithelial surface (Gulsen & Chauhan, 2005; Gulsen et al., 2005; Jung et al., 2013). The researchers have been successful in developing therapeutic contact lenses for extended drug delivery, while at the same time the transparency (optical), oxygen permeability, ion permeability, mechanical properties, and swelling behaviour of contact lenses was altered for comfort wear.

5. CONCLUSION
Advancements in the field of contact lenses drug delivery has been constituted lately, with controlled loading and sustained release. Various techniques have been employed for increasing the drug load and controlled release. Each technique may have some advantages and disadvantages with little effect on the mechanical and optical properties of the lens. Different lens materials and their requirement for ophthalmic use have effects on drug loading as well. The type of contact lenses and the technique of drug loading are found to affect the residence time of the drug. Comparatively, contact lenses provide an increased residence time at the surface of the eye for efficient therapy than the topical alternatives.

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