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RESEARCH PAPER

pHEMA as a Biomaterial for Artificial Cornea Applications: A short Study

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Abstract

Poly (2-hydroxyethyl methacrylate) (pHEMA) is widely recognized as a leading candidate for artificial cornea applications due to its exceptional optical clarity, mechanical properties, and biocompatibility. pHEMA's transparency and low light scattering make it an ideal material for corneal prostheses, which must closely mimic the natural cornea's ability to transmit light while maintaining structural integrity. This study provides a comprehensive examination of pHEMA's physical, chemical, and biological properties, fabrication techniques, and modifications tailored for corneal replacements. The inherent hydrophilicity of pHEMA allows for good tissue integration and hydration, which is essential for the maintenance of corneal function. Additionally, pHEMA exhibits favorable mechanical properties, including flexibility and strength, necessary for withstanding the dynamic forces placed on the cornea. However, key challenges remain in the development of pHEMA-based artificial corneas. One of the primary obstacles is its hydrophobicity after certain surface treatments or processing steps, which can compromise its biocompatibility. Additionally, the material's vulnerability to immune response, inflammation, and rejection by the host tissue remains a concern for long-term implantation. Mechanical durability, particularly the wear and tear associated with corneal movement during blinking, also requires improvement to ensure the longevity of the prosthesis. To address these challenges, this paper discusses cutting-edge solutions such as micro- and nanofabrication techniques that enhance the material's surface properties and mechanical performance. Surface treatments, including plasma modification, chemical crosslinking, and the incorporation of biomolecules, have been explored to improve pHEMA's hydrophilicity, reduce the immune response, and enhance cellular adhesion. Furthermore, biofunctionalization strategies that promote the integration of pHEMA with surrounding tissue and support epithelial and endothelial cell growth are considered crucial for improving long-term clinical outcomes. The development of composite materials and pHEMA blends with other polymers or bioactive molecules is also examined as a strategy to enhance the overall performance of artificial corneas. These approaches can optimize pHEMA's mechanical durability and reduce the risk of complications such as tissue rejection and graft failure. This paper aims to serve as a foundation

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for further innovation in the design and development of artificial corneas. It provides an in-depth look into the various facets of pHEMA's potential, while also identifying critical areas of research that require attention in order to overcome current limitations. By advancing the understanding of pHEMA's properties and exploring novel fabrication methods, this study contributes to the ongoing efforts to create more effective and sustainable solutions for corneal transplantation.

Keywords: Poly (2-hydroxyethyl methacrylate); Mechanical properties; Immune response; Natural cornea

1. Introduction

Corneal blindness is one of the leading causes of visual impairment worldwide, affecting an estimated 12.7 million people annually. Common causes include trauma, infections such as keratitis, and degenerative diseases like Fuchs' dystrophy [1]. In many cases, corneal transplantation remains the primary treatment, relying on donor tissues to restore vision. However, the global shortage of corneal donors creates a significant barrier to addressing this widespread issue. For instance, studies indicate that for every 70 corneas needed, only one donor cornea is available in regions like Africa and Southeast Asia [2]. This disparity highlights the urgent need for alternative solutions to address corneal blindness on a scale. Artificial corneas, also known as keratoprostheses, have emerged as viable alternatives to donor transplantation. These synthetic devices are designed to replace the natural cornea, restoring its refractive and protective functions [3-11]. While existing keratoprostheses, such as the Boston Keratoprosthesis, have shown success in specific patient populations, they are associated with challenges such as poor biocompatibility, device extrusion, and tear film instability [12]. These limitations underscore the need for novel materials that closely mimic the native cornea's properties, ensuring long-term success and broader applicability. Poly (2-hydroxyethyl methacrylate) (pHEMA) has garnered significant attention as a biomaterial for artificial corneas due to its unique combination of properties [13]. Originally developed in the 1960s for contact lenses, pHEMA is a hydrophilic polymer capable of high-water retention, optical clarity, and biocompatibility [14]. These attributes make it particularly suited for applications requiring transparency and integration with biological tissues. Furthermore, its tunable mechanical properties enable researchers to adjust its stiffness, hydration levels, and porosity to meet the specific demands of corneal implants. Despite its promising attributes, pHEMA is not without challenges [15]. One critical limitation is the material's tendency to become hydrophobic after fabrication, reducing its ability to interact with cells and maintain hydration over time. This shift compromises its long-term performance in vivo. Additionally, pHEMA's mechanical properties must strike a delicate balance: the material must be strong enough to withstand intraocular pressure while remaining flexible enough to avoid damage to surrounding tissues. Addressing these challenges requires innovative fabrication techniques and surface modification strategies, which have been the focus of recent research. Recent advances in micro- and nanofabrication have enabled the creation of patterned pHEMA surfaces that mimic the cornea's native structure, improving both cellular integration and optical performance. For example, micropatterning techniques can replicate the stromal fibril arrangement, enhancing light transmission and tear film stability [16]. Additionally, researchers are exploring the incorporation of bioactive molecules and nanoparticles into pHEMA to mitigate inflammation, promote epithelial healing, and deliver therapeutic agents'

post-implantation. This paper aims to provide a comprehensive review of pHEMA's potential for artificial cornea applications, focusing on its chemical, physical, and biological properties. Key topics include [17]:

1. Advances in fabrication techniques, such as photopolymerization and 3D bioprinting.
2. Surface modification strategies to overcome hydrophobicity and enhance biocompatibility.
3. Emerging applications of patterned pHEMA for tear film stabilization and cellular adhesion.
4. Long-term challenges, including immune response and mechanical stability, and proposed solutions.

By consolidating current knowledge and highlighting areas for future research, this study seeks to advance the development of pHEMA-based artificial corneas, ultimately addressing the unmet needs of patients with corneal blindness.

2. Properties of pHEMA

pHEMA is a hydrophilic polymer synthesized through the polymerization of 2-hydroxyethyl methacrylate (HEMA) monomers. Its chemical structure features hydroxyl groups that contribute to water absorption and crosslinked methacrylate units that provide mechanical stability. pHEMA can retain water content up to 38% by weight, ensuring optical transparency [18]. However, its hydrophilicity decreases over time due to surface rearrangement, resulting in hydrophobicity that can impede its long-term performance. pHEMA exhibits a Young's modulus similar to that of soft tissues (~0.1–0.5 MPa). The mechanical strength can be adjusted through crosslinking density, allowing optimization for specific applications. With a refractive index close to 1.43, pHEMA closely matches the human cornea. Its optical clarity is maintained by minimizing microphase separation during synthesis [19]. Biocompatibility studies indicate minimal immune response to pHEMA implants. However, the polymer's interaction with cells and proteins can vary depending on its surface chemistry and modifications [20].

3. Fabrication Techniques

3.1. Bulk Polymerization

The simplest method involves thermal or UV polymerization of HEMA monomers in the presence of crosslinking agents like ethylene glycol dimethacrylate (EGDMA). Bulk polymerization is cost-effective but may lead to inhomogeneous crosslinking [21].

3.2. Photopolymerization

UV-induced polymerization offers precise control over polymer structure and crosslinking density. This technique is widely used for creating patterned hydrogels [22].

3.3. Micropatterning with PDMS

Micropatterns such as pores, ridges, and dots are transferred onto pHEMA using PDMS molds. These patterns enhance cellular integration and tear film stability [23].

3.4. Surface Modification

Surface hydrophobicity, a challenge for long-term applications, can be addressed through [24]:

- **Plasma Treatment**: Increases surface energy and hydrophilicity.
- **Grafting**: Covalent attachment of hydrophilic polymers like PEG to reduce protein adsorption and biofouling.

3.5. 3D Bioprinting

Advanced fabrication using 3D bioprinting allows the creation of complex, patient-specific corneal implants with integrated microstructures.

4. Biological Considerations

The biological performance of artificial corneas is crucial to their success in restoring vision and integrating seamlessly with host tissues. Poly (2-hydroxyethyl methacrylate) (pHEMA) presents promising characteristics in this context, but its long-term efficacy depends on optimizing cellular interactions, immune compatibility, and mechanical stability [25].

4.1. Cellular Response

The corneal epithelium serves as a critical barrier and light-transmitting layer in the eye. For artificial corneas, successful epithelialization—where epithelial cells adhere to, proliferate on, and differentiate across the surface—is vital for restoring function and preventing complications like infection or stromal exposure [26].

4.2. Micropatterned pHEMA for Enhanced Integration

Micropatterning pHEMA with structures such as grooves, ridges, or dots mimics the natural extracellular matrix (ECM) of the cornea. These patterns provide physical cues that guide epithelial cell alignment and migration, a process known as contact guidance. Research has shown that epithelial cells cultured on micropatterned pHEMA exhibit improved alignment, proliferation, and adhesion compared to non-patterned surfaces. The patterns also enhance tear film stability by promoting uniform surface hydration, which is essential for maintaining corneal transparency and comfort as shown in Fig. 1 [27].

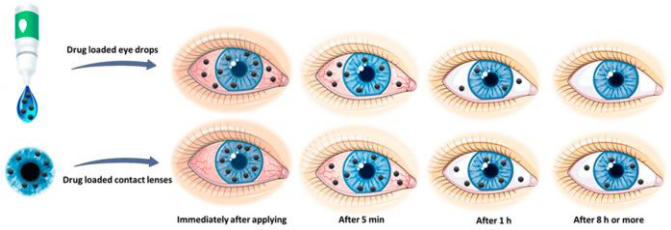

Figure 1:A schematic illustration highlighting the variation in drug release duration between contact lenses and traditional topical formulations [27]

4.3. Surface Chemistry's Role in Cellular Response

Unmodified pHEMA surfaces can exhibit limited cell adhesion due to their hydrophilic yet non-bioactive nature. To address this, chemical modifications are applied [28]:

- **Covalent grafting of cell-adhesive peptides** such as arginyl-glycyl-aspartic acid (RGD) sequences enhances integrin-mediated cell adhesion.
- **Incorporating ECM-derived molecules**, such as laminin or fibronectin, improves cellular interactions and mimics the natural corneal microenvironment.

By optimizing these physical and chemical properties, pHEMA-based implants can better support epithelialization, leading to faster healing and improved integration with surrounding tissues.

4.4. Immune Compatibility

While pHEMA exhibits low inherent immunogenicity, as evidenced by its historical use in contact lenses as shown in Fig. 2, and implants, the long-term presence of synthetic materials in the eye can trigger mild inflammatory responses. These responses, though typically non-severe, can compromise the implant's longevity and performance [27].

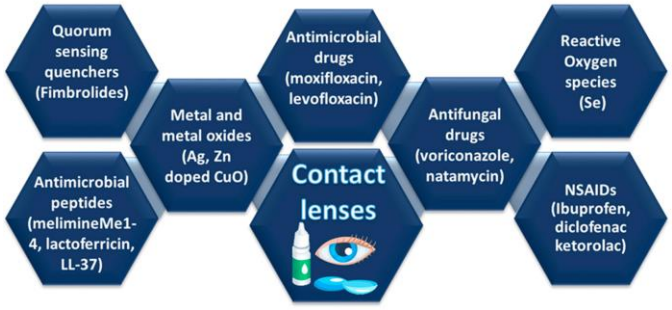

Figure 2: 2 Strategies for fabricating contact lenses with antimicrobial properties [27]

5. Inflammatory Triggers in pHEMA Implants

The surface of pHEMA can adsorb proteins from the tear film, leading to an inflammatory cascade. This is particularly concerning if the adsorbed proteins undergo denaturation, signaling immune cells [29]. Poorly integrated surfaces or rough edges may mechanically irritate the surrounding tissues, exacerbating inflammation. Coatings with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), or immunomodulatory molecules can reduce local inflammation. For example, dexamethasone-releasing coatings on pHEMA implants have been shown to significantly mitigate inflammatory responses in preclinical studies [30]. Incorporating bioactive molecules like cytokines (e.g., interleukin-10) or growth factors (e.g., epidermal growth factor) into the pHEMA matrix can promote a pro-healing environment. These molecules regulate immune cell activity and support tissue regeneration around the implant. Hydrophilic coatings, such as those using polyethylene glycol (PEG) or zwitterionic polymers, create a steric barrier that reduces protein fouling. These modifications have been shown to suppress the activation of immune cells, thereby improving implant tolerance [31]. By addressing the inflammatory triggers and leveraging advanced coatings, pHEMA implants can achieve long-term biocompatibility.

6. Degradation and Long-Term Stability

pHEMA's non-degradable nature makes it inherently suitable for permanent implants, ensuring that the material retains its structural integrity over time. However, external environmental factors and prolonged use in the dynamic ocular environment can still degrade its mechanical and optical properties [32]. Continuous exposure to ultraviolet (UV) light can degrade pHEMA's polymeric chains, leading to discoloration and loss of transparency. Incorporating UV-blocking agents during fabrication can mitigate this risk. The cornea is subjected to constant mechanical forces from blinking and intraocular pressure. Over time, these forces may cause microcracks in the pHEMA matrix, compromising its structural stability and increasing the risk of implant failure. Reinforcing pHEMA with nanomaterials like graphene oxide or silica nanoparticles has been shown to enhance its mechanical resilience. pHEMA's performance is highly dependent on its hydration state.

Prolonged exposure to fluctuating hydration levels can cause volumetric swelling or shrinkage, altering its refractive index and compromising optical clarity. Crosslinking optimization during fabrication can control swelling behavior and ensure long-term dimensional stability.

6.1. Strategies for Long-Term Stability:

- **Surface Coatings for UV Protection:** Applying thin UV-blocking layers to the surface of pHEMA can preserve its optical clarity and mechanical integrity.
- **Nanocomposite Reinforcement:** Incorporating nanoscale fillers not only improves mechanical properties but also enhances resistance to environmental degradation.
- **Hydration-Stabilizing Additives:** Embedding hydrophilic polymers like poly(vinyl alcohol) (PVA) into the pHEMA matrix can stabilize water retention and minimize swelling variability.

Conclusion

pHEMA represents a versatile and promising material for artificial corneas. Advances in fabrication techniques and surface modification strategies have addressed many challenges, paving the way for clinical adoption. Future research should focus on integrating advanced biomaterials and leveraging computational tools to design next generation keratoprostheses.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

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