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Current Trends In The Hydrogel Technology

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Abstract

The main matter which is involved in this review article is hydrogel ; having a unique ability to absorb water and expand, effectively entrapping a considerable amount of water within their structure while remaining insoluble in water. These materials possess the remarkable ability to undergo substantial volume transitions, leading to significant alterations in size when subjected to a wide array of physical and chemical stimuli. The hydrophilicity of the polymer network is conferred by the presence of polar functional groups present within the structure. These hydrogels possess properties such as high water content, porosity, and a soft consistency, which enable them to closely mimic natural living tissues. The term "hydrogel," as noted by Lee, Kwon, and Park, can be traced back to an article published in 1894. Over the years, there has been a continuous evolution in the objectives, aspirations, and the diversity of materials employed in this field. Hydrogels are classified into various types on the basis of source, polymeric composition, biodegradability, configuration, physical appearance. Hydrogel-based delivery devices have various applications including wound healing, the creation of cosmetic products, designing contact lenses, ocular treatments, as well as for transdermal and topical applications.

INTRODUCTION

This review focuses on hydrogels, often referred to as hydrophilic gels or aqua gels [1]. Hydrogels can be defined as materials with the unique ability to absorb water and expand, effectively entrapping a considerable amount of water within their structure while remaining insoluble in water. Their water-absorption capacity can range from a minimum of 10-20% of their dry weight to an extraordinary expansion of thousands of times their initial weight in water. The past decade has witnessed a surge of interest in hydrogels due to their exceptional properties and extensive array of applications [2]. Functioning as three-dimensional networks of hydrophilic polymers, hydrogels exhibit a striking capability to undergo reversible swelling and contracting in response to water, efficiently retaining substantial amounts of liquid when in their swollen state. These networks consist of interlinked polymer chains, where water functions as the dispersing medium [1]. The specific characteristics of these polymer networks are contingent upon the composition and arrangement of constituent monomers, as

well as the method of synthesis. The notable diversity in preparation techniques and available starting materials for hydrogel synthesis empowers their utilization across a wide spectrum of applications [3]. Hydrogels can be precisely engineered to exhibit controlled responses, allowing them to contract or expand in reaction to changes in their external environment. These materials possess the remarkable ability to undergo substantial volume transitions, leading to significant alterations in size when subjected to a wide array of physical and chemical stimuli. Physical stimuli involve factors such as temperature, electric fields, sound waves, pressure, and light, whereas chemical stimuli involve variations in pH, ionic strength, and solvent composition. The response of hydrogels, involving swelling or de-swelling, to shifts in their surrounding environment can be so profound that it may even lead to explosive behaviour. This phenomenon is often described as a phase transition or volume collapse [4]. Hydrogels find their applicability as biomaterials due to their distinct properties, including high water content, soft and elastic consistency, and weak adhesive forces with water or biological fluids. These attributes make them particularly suitable for use within biological contexts [5]. Depending on the presence of functional groups in their structure, hydrogels can be categorized as charged or non-charged. Charged hydrogels typically exhibit changes in their swelling behaviour in response to shifts in pH, and they are known to undergo alterations in shape when subjected to electric fields [6]. The hydrophilicity of the polymer network is conferred by the presence of polar functional groups, which include entities such as hydroxyl (–OH), amino ($–NH_2$), carboxyl (–COOH), and sulfonic acid ($–SO_3H$) groups[7]. Researchers have extensively explored a diverse range of natural polymers like polypeptides, polysaccharides, and DNA, as well as synthetic polymers such as polyacrylamide and poly (vinyl alcohol), to synthesize hydrogels endowed with appealing properties. These hydrogels can take on various physical forms, including slabs, microparticles, nanoparticles, coatings, or films.

Consequently, hydrogels have found widespread use in both clinical applications and investigative medicine, encompassing a wide spectrum of uses such as tissue engineering and regenerative medicine [8], diagnostics [9], cellular immobilization [10], and the creation of barrier materials to manage biological adhesions [11]. Since the pioneering work of Wichterle and Lim in 1954, who introduced the concept of synthetic hydrogels [12], these hydrogel technologies have opened up avenues for a wide range of practical applications. These applications span diverse fields, including hygienic products [13], agriculture [14], drug delivery systems [13,15], sealing applications [13], artificial snow production [13], coal dewatering processes [16], incorporation as food additives [17], pharmaceutical development [18], advancements in biomedical applications [19], and the creation of highly sensitive biosensors [20].

In brief, hydrogels can be described as hydrophilic polymeric networks with a three-dimensional structure capable of efficiently absorbing significant quantities of water or biological fluids. These hydrogels possess properties such as high water content, porosity, and a soft consistency, which enable them to closely mimic natural living tissues. This resemblance to biological tissues sets them apart from other types of synthetic biomaterials. Depending on their composition, hydrogels can exhibit either long-lasting chemical durability or they may gradually degrade and dissolve over time [21]. Researchers have investigated the potential of hydrogel formulations comprising various combinations of polymers for their efficacy as drug delivery systems. The strategic blend of natural and synthetic polymers offers a dual advantage of enhanced mechanical stability and improved biocompatibility, capitalizing on the synergistic properties of these diverse materials. Notably, an innovative approach involving the combination of collagen and hyaluronic acid within interpenetrating network (IPN) hydrogels has been pursued. This initiative aims to bolster the mechanical robustness of natural polymers while simultaneously addressing the limitations inherent in synthetic polymers [22].

These hydrogels are meticulously crafted from materials such as gelatin, polysaccharides, cross-linked polyacrylamide polymers, polyelectrolyte complexes, as well as polymers or copolymers derived from methacrylate esters. Crucially, these hydrogels exhibit insolubility in water and can be found in various forms, including both dry or hydrated sheets and as hydrated gels. Particularly, they find application within drug delivery systems designed for single-use scenarios. Hydrogels can be defined as intricate cross-linked polymer networks with the remarkable ability to intelligently respond to variations in environmental stimuli, including changes in ionic strength, pH, temperature, the presence of enzymes, and electric fields. Depending on these fluctuations, hydrogels can undergo controlled swelling or shrinking reactions. When in their swollen state, these hydrogels exhibit a soft and rubbery consistency that closely resembles living tissue, showcasing outstanding biocompatibility. This unique set of properties has sparked significant interest in hydrophilic gels, commonly referred to as hydrogels, particularly within the field of pharmaceutical and biomedical engineering. Their potential for use in these fields holds considerable promise [23].

Numerous combinations of polymers have been incorporated into hydrogel formulations to explore their viability as drug delivery systems. The strategic blending of both natural and synthetic polymers offers the dual benefits of enhanced mechanical stability and improved biocompatibility, making use of the synergistic links

is fundamental to these distinct materials. An intriguing attempt has involved the amalgamation of collagen and hyaluronic acid within interpenetrating network (IPN) hydrogels, undertaken with the objective of strengthening the mechanical integrity of natural polymers and simultaneously easing the limitations associated with synthetic counterparts. This initiative seeks to achieve a delicate equilibrium between the inherent strengths of these different polymer types, thereby facilitating the development of advanced delivery systems that maintain their combined advantages. [24]. In certain cases, hydrophobic monomers are introduced into the process of hydrogel preparation as a means of tailoring the properties of the hydrogel to suit specific applications. Typically, hydrogel preparation involves the incorporation of three fundamental components: monomers, initiators, and cross-linkers. These elements collectively contribute to the synthesis and formation of hydrogels [25].

HISTORY

The term "hydrogel," as noted by Lee, Kwon, and Park, can be traced back to an article published in 1894. However, it is important to clarify that the substance described in that historical context does not align with the modern concept of a hydrogel. Rather, it was colloidal gel comprised of inorganic salts. Therefore, while the term itself has a historical origin, the material referred to in that context significantly differs from the understanding and characterization of hydrogels [26]. In the year 1954, the initial synthetic hydrogels were developed by Wichterle and Lim through the utilization of poly-2-hydroxyethyl methacrylate (pHEMA) [27]. This achievement was followed by the incorporation of hydrogels into the production of contact lenses, marking an early practical application of this material. [27,28]

Conventional approaches in skin tissue engineering have primarily concentrated on replicating the structural aspects of skin tissue to a limited extent. However, these methods often oversimplify the complex composition of skin tissues by dividing them into distinct layers such as the epidermis and dermis. While significant progress has been made in the department of skin tissue regeneration, there remains plenty room for further enhancements and refinements in achieving more optimal outcomes. [29-31]. As an example, skin substitutes have the potential not only to replicate the multi-layered structural characteristics of skin tissue but also to facilitate crucial functions like blood vessel formation and antibacterial properties, which actively contribute to promote the process of skin regeneration. Consequently, there arises a need for the advancement of more techniques within the department of skin tissue engineering. These refined methods should aim to faithfully reproduce the complex structure and function in natural skin tissue. Current advanced skin substitutes include hydrogels, acellular extracellular matrix, and electrostatic spinning [32,33]. Hydrogels demonstrate resemblance with the structure and properties of human skin tissue. Emerging applications for hydrogels today include device coatings [34], environmental engineering [35], soft robotics [36].

The evolution of hydrogels can be categorized into distinct phases, each representing significant advancements and development over time. The initial phase of hydrogel development, often referred to as the first generation, encompasses a broad spectrum of crosslinking techniques involving chemical modifications of monomers or polymers through initiators. The primary objective during this phase is the creation of materials with notable attributes, including high swelling capacity, favorable mechanical properties, and a relatively straightforward rationale [37]. The earliest documented instance of a crosslinked network material possessing distinct hydrogel characteristics emerged later, specifically in 1960, with the introduction of a polyhydroxyethylmethacrylate (pHEMA) hydrogel. This hydrogel was designed with the ambitious intention of enabling its use in permanent contact applications involving human tissues. Remarkably, hydrogels represent a pioneering class of materials that were initially developed for internal applications within the human body, marking a significant milestone in their history [38,39].

Subsequently, there was a notable upsurge in the volume of research belonging to hydrogels for biomedical applications, particularly during the 1970s and onward [26]. Over the years, there has been a continuous evolution in the objectives, aspirations, and the diversity of materials employed in this field, as highlighted by Buwalda and colleagues [12]. As the field progressed, a distinctive shift in focus emerged, giving rise to a second generation of hydrogel materials with an emphasis on responsiveness to specific external stimuli. This concept gained prominence, enabling hydrogels to exhibit tailored reactions in response to variations in factors like temperature, pH, or the concentration of particular molecules within a solution. These unique stimuli-driven responses can be harnessed to trigger specific events, such as initiating the polymerization of the material, facilitating drug delivery mechanisms, or even inducing the formation of pores in situ [37].

Eventually, the evolution of hydrogel technology led to the emergence of a third generation, characterized by a distinct focus on exploring and advancing complexed materials. An example.e of such interactions involves the combination of polyethylene glycol (PEG) and polylactic acid (PLA). This new phase represents a

significant shift in research focus, aiming to harness the potential of these stereo complexed materials for diverse applications within the field of hydrogel technology [40,41]. Following the contributions of Wichterle and Lim in 1960 regarding the development of crosslinked hydrogels [39], these materials have gained considerable attention from the biomaterial research community. The hydrophilic nature of hydrogels, with their inherent capacity for potential biocompatibility, has delivered them a subject of enduring fascination and significance among biomaterial scientists over the span of several years [42]. 1980, Lim and Sun's seminal and influential work marked a significant milestone by successfully showcasing the application of calcium alginate microcapsules for the encapsulation of cells. Subsequently, during the 1980s, Yannas and collaborators [43] extended this research by incorporating natural polymers like collagen and shark cartilage into hydrogels, thereby creating artificial burn dressings with promising potential. Over the years, the interest in hydrogels, encompassing both natural and synthetic polymers, has endured, particularly in the field of cell encapsulation. In more recent times, these hydrogels have gained remarkable prominence in the emerging field of tissue engineering. They have emerged as matrices with exceptional appeal for mending and regenerating a wide spectrum of tissues and organs, further underscoring their significance [44]. Brief history of hydrogels is provided in the review [27].

SIGNIFICANT PROPERTIES OF HYDROGEL:

(4) **Swelling:**

Slight modifications in environmental factors have the potential to induce rapid and readily reversible transformations in hydrogels. These alterations in the surroundings, such as variations in electric signals, pH levels, temperature, or the introduction of enzymes or other ionic substances, can trigger modifications in the hydrogel's physical characteristics. These alterations are by comparing the weight of the hydrogel in its dried state and its swollen state, subsequently allowing for the calculation of either water absorption or the volume of solvent absorbed. Both of these measurements are expressed as percentages and provide insights into the hydrogel's responsiveness to changing conditions.

WU = swollen weight – dry weigh/dry weight × 100

V.A.S = swollen weight – dry weigh/ water density × 10

Swelling assessment is crucial for hydrogel samples, measuring properties like crosslinking degree, mechanical properties, and degradation rate, enabling easy differentiation between crosslinked and non-crosslinked polymers [25].

(2) Porosity:

Pores can emerge within hydrogels through various mechanisms, one of which involves the occurrence of phase separation during the synthesis process. Alternatively, these pores might exist as smaller entities intricately distributed throughout the overall network structure of the hydrogel. Determining the average dimensions of pores, analyzing the distribution of pore sizes, and understanding the complex links between these pores stand as crucial characteristics of a hydrogel matrix. These aspects, while essential for comprehending the structural attributes of the hydrogel, often pose computational difficulties due to their complex nature. Collectively, they are confined within a single parameter known as "tortuosity," which serves as a comprehensive descriptor encompassing these pore-related features.

The distribution of pore sizes within hydrogels is significantly shaped by three key factors:

1. The concentration of chemical cross-links among the polymer strands, which is determined by the initial ratio of cross-linker to monomer.
2. The concentration of physical entanglements between the polymer strands, which is assessed based on the initial concentration of all polymerizable monomers present in the aqueous solution.
3. The net charge carried by the polyelectrolyte hydrogel, which is established by the initial concentration of cationic and/or anionic monomers within the hydrogel.

Together, these three factors play a pivotal role in defining the distribution of pore sizes within hydrogels.

Porosity is a morphological characteristic of a material that can be illustrated as the presence of void cavity inside the bulk.

Porosity % = $V_{pore}/V_{bulk} + V_{pore}$ x 100 [25]

(3) Biocompatible properties:

In the field of medicine, it's crucial that hydrogels are both compatible with living systems and free from harmful effects. To ensure their suitability for biomedical use, many of the polymers employed must undergo evaluations, like tests for toxicity within cells and in living organisms. Biocompatibility refers to a material's capability to function in a way that prompts an acceptable response from the body within a specific medical context.

Biocompatibility essentially comprises two fundamental components:
(a) Bio-safety encompasses not only the suitable reaction from the host organism on both systemic and local levels (within surrounding tissue), but also the absence of harmful effects like cytotoxicity, mutagenesis, and potential carcinogenesis.
(b) Bio-functionality refers to the capacity of a material to effectively carry out the particular function it is designed for.
Tissue engineering requires continuous interaction with the body during healing, regeneration, and scaffold degradation. Failure to meet this requirement may lead to fouled hydrogels, damage, and scarring to connected tissues. Toxic chemicals in synthetic hydrogel polymerization can hinder in vivo biocompatibility if conversion is not 100%. Initiators, organic solvents, stabilizers, emulsifiers, unreacted monomers, and cross-linkers can be toxic to host cells if they seep into tissues or encapsulated cells. For example, Irgacure 2959, a photo-initiator in free radical photopolymerizations, has been found to decrease cell viability when used in concentrations over 0.1% [45]. To eliminate harmful substances from gels that have already been formed, it is necessary to undertake different purification methods such as solvent washing or dialysis. The unique difficulty arises when scaffolds are formed in their intended location, commonly using oligomers and pre-polymers. In this scenario, the chemicals used to create the gel are introduced into the body while they are still in a pre-polymer solution, presenting a distinct challenge. The application of this method is optimal due to its minimally invasive nature. However, it demands careful consideration to guarantee the safety and acceptable lack of toxicity of all employed elements. While natural polymers are often seen as more biocompatible compared to synthetic counterparts, it's important to note that the synthetic cross-linkers and initiators utilized during the polymerization of naturally sourced monomers and pre-polymers can raise similar concerns about their potential toxicity as entirely synthetic hydrogels.
4) Mechanical Properties:
The mechanical characteristics have the potential to change and transform based on the material's composition and the extent of crosslinking present. It is possible to achieve a hydrogel with enhanced rigidity through increased crosslinking or to reduce its stiffness by subjecting it to heat, thus decreasing the degree of crosslinking. As the crosslinking degree rises, the hydrogel's strength also intensifies. Nevertheless, increased cross-linking results in reduced elongation percentages and the creation of hydrogels that are more prone to brittleness. Additionally, combining copolymerization with hydrophobic monomers for interpenetrating networks (IPNs), as well as grafting onto a hydrophobic substrate, enhances the mechanical attributes of the resulting composite or nanocomposite materials. It is possible to engineer hydrogels to replicate the transport and mechanical characteristics of natural soft tissues. However, most hydrogels are not stable in both dehydrated and swollen states. In numerous cases, the process of drying gives rise to cracks within the hydrogel structure. The inclusion of highly absorbent salts in the hydrogel matrix or enveloping the hydrogel within an elastomeric substance are approaches aimed at mitigating the challenges connected with drying procedures. A more recent and efficient technique has been introduced to create hydrogels that can withstand both swelling and drying conditions. In this study, researchers developed a double hydrophobic coating using a hydrophobic polymer and a viscous oil through a quenching process. This approach resulted in the formation of a 200 μm thick layer over the hydrogel. The adjustments in mechanical attributes are influenced by a multitude of factors. For example, when examining white gelatin, a noticeable enhancement in Young's Modulus is observed due to the process of crosslinking [25,3].

CLASSIFICATION:

(1) Classification based on source

Hydrogels can be categorized into two divisions according to their sources.
(a) Natural hydrogels- Natural hydrogels are biodegradable and biocompatible which possess
favorable properties for cell adhesion. Two primary categories of natural polymers are commonly employed in the creation of these hydrogels. These categories encompass proteins like collagen, gelatin, and lysozyme (LYZ), as well as polysaccharides including hyaluronic acid (HA), alginate, and chitosan (Cts).
(b) Synthetic hydrogels: In comparison to natural hydrogels, they hold a greater utility due to their capacity for customization, allowing for a broader spectrum of mechanical and chemical attributes than their naturally derived counterparts. Among the extensively employed materials in biomedical applications, hydrogels based on polyethylene glycol (PEG) constitute a notable category. This preference is due to their non-toxic nature, compatibility with biological systems, and minimal likelihood of eliciting an immune response.
(c) Hybrid hydrogels: They are a fusion of hydrogels derived from both natural and synthetic polymers. In order to harness the benefits offered by both synthetic and natural hydrogels, various naturally occurring

biopolymers such as dextran, collagen, and chitosan have been amalgamated with synthetic polymers like poly(N-isopropylacrylamide) and polyvinyl alcohol [25].

(2) Classification based on polymeric composition

The method of fabrication results in the creation of primary categories of hydrogels. These can be illustrated as follows:

(a) Homopolymeric hydrogels: Polymer networks originating from a single type of monomer, constituting the fundamental building blocks of any polymer network, form the basis of homopolymers. Depending on the specific monomer and the method of polymerization, homopolymers can exhibit a crosslinked structural framework. Apart from their use in contact lenses, these materials find application in the creation of artificial skin and burn dressings, ensuring favourable conditions for wound healing. They also play a pivotal role in endeavours such as the regeneration of bone marrow and spinal cord cells, the fabrication of scaffolds to encourage cell adhesion, and the production of synthetic cartilage.

(b) Copolymeric hydrogels: These structures are composed of a minimum of two distinct types of monomer species, wherein at least one component is hydrophilic. These components are organized in a random, block, or alternating arrangement along the polymer network's chain.

(c) Multipolymer hydrogels: These are alternatively known as interpenetrating polymeric hydrogels (IPN), a significant category of hydrogels. They are composed of two distinct and self-contained cross-linked components, which can be either synthetic or natural polymers, interwoven within a network structure. In semi-IPN hydrogels, one of these components is a polymer that has been cross-linked, while the other component is a polymer that has not undergone cross-linking.

(3) Classification based on biodegradability

(a) Biodegradable hydrogels: Hydrogels possess biodegradability, and several naturally occurring polymers like Chitosan, fibrin, and agar are also biodegradable. Synthetic biodegradable polymers include examples like poly(aldehyde guluronate), polyanhydrides, and poly(N-isopropyl acrylamide).

(b)Non-Biodegradable hydrogels: A variety of vinyl-based monomers or macromers, such as 2-hydroxyethylmethacrylate (HEMA), methoxyl poly(ethylene glycol) (MPEG), 2-hydroxypropyl methacrylate (HPMA), and acrylamide (AAm), find extensive use in crafting non-biodegradable hydrogels [23].

(4) Classification based on configuration:

This classification of hydrogels relies on their physical structure and chemical composition which can be illustrated as follows:

(a) Amorphous (non-crystalline).

(b) Semi crystalline: A complex mixture of amorphous and crystalline phases.

(c) Crystalline [46]

(5) Classification based on physical appearance:

The presentation of hydrogels in forms like matrix, film, or microspheres is determined by the specific polymerization method utilized during the formulation process. Hydrogels can be categorized into four distinct groups based on whether electrical charge is present or absent within the crosslinked chains:

(a) Nonionic (neutral).

(b) Ionic (including anionic or cationic).

(c) Amphoteric electrolyte (ampholytic) comprising both acidic and basic groups.

(d) Zwitterionic (polybetaines) consisting of both anionic and cationic groups in each structural repeating unit [46]

(6) Classification based on responses

1. biochemical responsive hydrogels

(a) antigen responsive

(b) enzyme responsive

© ligand responsive

2. physically responsive hydrogels

(a) temperature

(b) Pressure

© Light

(d) Electric field

©Magnetic field
3. chemically responsive hydrogels
(a) pH responsive
(b) glucose responsive
© oxidant responsive [47]

APPLICATION:

Hydrogel-based delivery devices have various applications including wound healing, the creation of cosmetic products, designing contact lenses, ocular treatments, as well as for transdermal and topical applications. Hydrogels can be employed at various sites for drug delivery purposes.

1. Wound healing
Due to their capacity to retain water, hydrogels exhibit the ability to capture and hold wound exudates. Hydrogels formulated from substances like gelatin and sodium alginate demonstrate the capability to cover and safeguard wounds, effectively preventing bacterial infections from occurring [23]. In the realm of cartilage defects treatment, an innovative approach involves the use of a modified polysaccharide found in cartilage to create hydrogels. This polysaccharide is chemically modified with methacrylate and aldehyde groups, allowing it to interact with skin tissue proteins. Meanwhile, the methacrylate groups form cross-links with the chondroitin disaccharide backbone, resulting in the formation of a network. Within this network, chondrocyte cells can be released to facilitate healing. Honey hydrogels have also been employed to expedite wound healing. These hydrogels consist of a matrix cross-linked with honey, offering a highly acceptable, easily manageable, and transparent system for wound treatment. Furthermore, a hydrogel combining gelatin and polyvinyl alcohol (PVA), along with a blood coagulant, has been developed. This cell-adhesive hydrogel has proven to be more effective in controlling blood coagulation compared to its gel or ointment counterparts [48].

2. Cosmetic preparations
For cosmetic reasons, hydrogel implants have been utilized for breast enhancement. When placed inside the body, these hydrogels expand due to the presence of moisture and effectively retain water. These breast implants consist of a silicone elastomer shell and are filled with a hydroxyl propyl cellulose polysaccharide gel [47].

3. Ocular drug delivery
Hydrogels play a prominent role in ocular drug delivery systems, finding extensive application in this field. Both rigid and soft contact lenses are frequently composed of hydrogel films. In the context of ocular drug delivery, in-situ forming hydrogels are particularly appealing due to their capacity to be administered as a liquid and then transform into a gel for sustained release after dosing [23]. To achieve sustained drug delivery for drugs like pilocarpine and timolol in ocular applications, gel-forming polymers like xyloglucan have been employed. For comprehensive drug absorption through the cornea, hydrogels containing poly hydroxyethyl methacrylamide (pHEMA), N, N-dimethyl acrylamide (DMAAm), and 2-(N-ethyl per fluorooctane sulfonamide) ethylacrylate (FOSA) have been utilized for ocular delivery. Successful delivery of drugs such as diclofenac and phenaramine maleate has been achieved through hydrogel-based systems [48].

4. contact lenses
Contact lenses made from hydrogels offer an ideal foundation for producing micro-optical arrays that can adjust their focal lengths dynamically. These arrays can be manufactured in a cost-effective and scalable manner. The fabrication methods for micro lens arrays encompass techniques like photolithography, photo-thermal patterning, and the assembly of polymer particles with subsequent melting. However, these methods often entail precise and multiple fabrication steps. Moreover, the resulting micro lens arrays typically consist of optical components with fixed focal lengths, relatively large diameters, and slow rates of focal length alteration. An alternative approach involves the creation of ordered micro lens arrays through the electrostatically driven assembly of poly(NIPAM-AA) microgels onto glass substrates that have been functionalized with (3-aminopropyl)trimethoxysilane. Under pH conditions of 6.5, the electrostatic attraction between the anionic AA groups of the microgels and the amine groups on the substrate facilitates particle binding to the surface. The lensing capabilities of the microgels on the substrate arise from their hemispherical shape and the refractive index contrast between the contracted microgel and the surrounding medium. A higher contrast in refractive indices results in lenses with shorter focal lengths and improved lens power. More recently, there have been

reports on the fabrication of arrays of photoswitchable microlenses. These arrays were crafted by depositing poly(NIPAM-AA) microgels onto surfaces coated with gold nanoparticles. The system was selectively heated through irradiation at a wavelength of 532 nm, which corresponds to the surface plasmon modes of the gold nanoparticles. Plasmon excitation caused energy to transfer to the microgels in the form of heat. The modulation of the focal length of the micro lens arrays was studied by illuminating them with laser lights of varying intensities at different temperatures and pH levels. Notably, enhanced focusing was achieved when the excitation of the gold nanoparticles led to microgel heating beyond the volume phase transition temperature of the poly(NIPAM-AA) microgels. Given their swift volume transitions, straightforward fabrication techniques, and the dynamic adjustability of focal lengths, microgel-based microlens arrays exhibit substantial promise as devices for advancing micro-optics technology [47].

5. Drug delivery system

Integrating biocompatible nanoparticles into the structure of hydrogels can enhance both cell adhesion and the therapeutic capabilities of the hydrogels. An injectable hydrogel, infused with gold and laponite nanoparticles, was evaluated to enhance the clinical effectiveness of cardiovascular regeneration. The inclusion of electrically conductive substances and nanoparticles into the extracellular matrix (ECM) of the myocardium was proposed as a strategy to augment the enduring functional traits of cardiomyocytes.

6. Oral delivery

Hydrogels utilized in oral therapeutic systems need to exhibit a range of desirable qualities, including biocompatibility, the ability to accommodate various active substances, adjustable characteristics, targeted delivery, and controlled release of both synthetic drugs and biotherapeutics. These attributes serve the purpose of facilitating treatments that are localized or systemic in nature. Notably, pH-sensitive hydrogels have demonstrated their efficacy in oral dosage forms containing chemotherapeutic agents, insulin, calcitonin, and interferon-β. Research findings have indicated that orally administered chemotherapeutic agents yield enhanced effectiveness while minimizing adverse effects when compared to parenteral administration. As a practical example, Zilactin-B Gel, a commercially available product, is utilized as a local anesthetic for minor oral issues. It comprises hydroxypropyl cellulose polymers with benzocaine serving as the active ingredient [49].

7. Transdermal Delivery

Transdermal drug delivery represents a significant approach for administering drugs through the skin's surface, allowing for targeted local or systemic effects [49]. In the realm of wound dressing, swollen hydrogels can serve as controlled release devices. Hydrogel-based formulations are being investigated for transdermal iontophoresis, aiming to improve the permeation of substances such as hormones and nicotine [23]. Notably, antifungal solutions like cotrimazole have been developed into hydrogel formulations for addressing vaginitis. These formulations have demonstrated enhanced absorption compared to conventional cream-based approaches [50].

8.Topical drug delivery

Hydrogels have been utilized as carriers for delivering active substances, such as Desonide, a synthetic corticosteroid renowned for its anti-inflammatory properties. These hydrogels, formulated as an alternative to conventional creams, are designed to enhance patient adherence to treatment. Remarkably, these hydrogels possess moisturizing qualities, thereby enhancing concerns of skin scaling and dryness associated with this drug delivery approach [23]. Furthermore, in the domain of antifungal treatments, hydrogel formulations like cotrimazole have emerged for tackling vaginitis. Impressively, these formulations exhibit superior absorption compared to conventional cream-based counterparts [50].

(9) Tissue Engineering

Tissue engineering or regenerative medicine represents a rapidly advancing interdisciplinary domain focused on the integration of scaffolds, cells, and biologically active compounds to promote the recovery, maintenance, and enhancement of tissue functionality. Biomaterials play a pivotal role by providing a predefined three-dimensional porous framework within the specific anatomical site. This framework enables cells to adhere, proliferate, and spatially reorganize, ultimately facilitating the generation of fully functional new tissue. Additionally, biomaterials facilitate the transfer of cells and desired biological agents to targeted locations within the body. The creation of diverse scaffold shapes with adjustable pore sizes is of paramount importance for confining both bioactive substances and cells, serving various biomedical applications [51].

Moreover, an interconnected porous structure holds great significance, as it establishes channels for the transport of essential nutrients and signaling molecules to reach the cultured cells. Ideally, a biomaterial should be biodegradable and bioresorbable, ensuring the restoration of damaged tissue without inciting an inflammatory response. Consequently, biomaterials should initially provide mechanical support during early tissue development and subsequently initiate their own degradation as tissue growth progresses without hindrance. Recently, a comprehensive review detailing the structure, synthesis, properties, fabrication techniques, and applications of hydrogels in tissue engineering has been published [52].

DESIRED FEATURES OF HYDROGEL MATERIAL

The ideal hydrogel material should possess the following characteristics:
- Demonstrates the highest capacity for absorption (maximum equilibrium swelling) in saline solutions.
- Exhibits the appropriate absorption rate (optimal particle size and porosity) as required by the specific application.
- Shows exceptional absorbency under load (AUL).
- Maintains minimal levels of soluble content and residual monomers.
- Comes at an affordable cost.
- Displays remarkable durability and stability both during swelling and storage.
- Exhibits the utmost biodegradability without generating toxic byproducts upon degradation.
- Achieves pH-neutrality after swelling in water.
- Remains colorless, odorless, and entirely non-toxic.
- Possesses good photostability.

In cases where re-wetting is necessary, the hydrogel should have the capacity to either release the absorbed solution or retain it, as dictated by the specific application needs. This versatility is essential, such as in scenarios like agricultural or hygienic applications.

ADVANTAGES

(1) Owing to their substantial water content, they exhibit a flexibility closely resembling that of natural tissue.
(2) Facilitates the timely release of medications or nutrients.
(3) They are characterized by biocompatibility, biodegradability, and the potential for injectability [25].
(4) Environmentally responsive hydrogels can detect alterations in pH, temperature, or metabolite concentration, triggering the release of their payload in response to such changes [53].
(5) Additionally, hydrogels boast favorable transport properties and are amenable to easy modifications[25].

FUTURE PERSPECTIVES AND CHALLENGES

Over the past few decades, numerous efforts have been dedicated to the advancement of targeted drug delivery systems. These systems aim to facilitate drug transportation to specific sites, organs, tissues, cells, or even organelles within the body, with the intent of enhancing therapeutic outcomes. In this pursuit, there is a significant exploration of self-assembled nanocarriers designed to actively target overexpressed antigens or receptors found in tumor cells. This strategy holds immense promise as a pivotal approach to treatment. The application of hydrogel-based biosensors has been extensively investigated across a range of biomedical contexts, including the detection of cell metabolites and pathogens, tissue engineering, wound healing, cancer monitoring, and the identification of low-molecular-weight endogenous ligands like glucose, lactate, urea, and cholesterol [54]. Notably, molecular imprinting techniques employing biological molecules in conjunction with monomers and cross-linking agents have been employed in biosensor fabrication. In current times, substantial attention is being directed towards the fabrication of 3D-printed materials utilizing hydrogels [55]. This integration of nanotechnology and dynamic methodologies, such as 3D printing, into tissue engineering systems has the potential to bridge the existing gaps within in vitro tissue engineering models. An emerging avenue in hydrogel-based bioprinting involves the creation of cell-laden scaffolds via 3D printing. This innovative approach seeks to develop structures with anatomical dimensions, intricate tissue architecture, and tissue-specific functionalities, thereby contributing to the evolution of tissue engineering techniques.

CONCLUSION

In recent times, numerous hydrogel-based networks have been tailored and customized to cater to various application requirements. When exposed to an aqueous solution, these hydrogels exhibit the capacity to swell.

This comprehensive review delves into the categorization of hydrogels based on differing criteria, encompassing their physical and chemical attributes, as well as their versatile applications. The findings from this study highlight the remarkable attributes of hydrogels, positioning them for abundant future applications as cutting-edge biomaterials in the next generation.

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