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Schiff-Base Thiadiazole-Modified Hydrogels: A Comprehensive Review of Biomedical Applications

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Abstract

Hydrogels are among the most versatile material classes used in biomedical applications. The material is of considerable interest in various fields of medicine due to its excellent features, such as high-water content, biocompatibility, and adjustable mechanical properties. The highlighted study thoroughly reviews Schiff-base thiadiazole-modified hydrogels as a novel functional material class, emphasizing their applicability in medical science. The addition of the Schiff-base and free thiazole groups to the hydrogel matrix introduces new antimicrobial activity, drug delivery, and bioadhesive attributes. An elaborate description of the methods employed to copolymerize thermoresponsive hydrogels with carbazole of thiadiazole as a binding group through free radical polymerization and visible light initiation is given under the first step of this general approach. The section on these hydrogels' physical and chemical properties was then added with a bias on morphological characterization, water uptake studies, and mechanical properties of the materials. After that, the discussion on more applications commenced, and among these, the following sections study them in the field of life-saving biomedical devices such as wound healing, tissue engineering, delivery of drugs, and biosensing prepared biosensing. A key emphasis is given to those interaction modes between Schiff-base thiadiazole groups and the biological systems that fulfil the hydrogels' healing mechanisms. These interaction modes, which include [specific modes], play a crucial role in the hydrogels' healing mechanism. The mentioned scholarship, in addition, dwells on the issues and barriers of such materials and gives thorough and valid judgements about the present and future of the matter. This review and the hard evaluation provide a thorough insight into Schiff-base thiadiazole-modified hydrogels' transformative impacts across the entire biomedicine area. A new approach is achieved by this review, in which the audience is made conscious and fully informed by presenting the most recent discoveries concerning the potential of Schiff-base thiadiazole-modified hydrogels to bring about innovative biomedical applications.

Keywords: Hydrogels, Schiff-Base, Thiadiazole, Biomedical Application.

الهلاميات المائية المعدلة بقواعد شيف ومركبات الثياديازول: مراجعة شاملة للتطبيقات الطبية الحيوية

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الخلاصة:

تُعد الهلاميات المائية (Hydrogels) من أكثر الفئات المادية تنوعًا واستخدامًا في التطبيقات الطبية الحيوية. يحظى هذا النوع من المواد باهتمام كبير في مجالات طبية مختلفة نظرًا لخصائصه الممتازة مثل المحتوى المائي العالي، والتوافق الحيوي، والخصائص الميكانيكية القابلة للتعديل. تسلط الدراسة الضوء على مراجعة شاملة للهلاميات المائية المعدلة بقواعد شيف ومركبات الثياديازول كفئة جديدة من المواد الوظيفية، مع التركيز على تطبيقاتها في العلوم الطبية. يؤدي

إضافة مجموعة قاعدة شيف ومجموعة الثيازول الحرة إلى مصفوفة الهلام المائي إلى إدخال خصائص جديدة مثل النشاط المضاد للميكروبات، ونقل الأدوية، والخصائص اللاصقة الحيوية.

تم تقديم وصف دقيق للطرق المستخدمة في تكوين البوليمر المشترك بين الهلاميات المائية الحساسة للحرارة ومركب الكربازول للثيادايازول كمجموعة ربط عبر بلمرة الجذور الحرة وتحفيز الضوء المرئي ضمن الخطوة الأولى من التفاعل. تم بعد ذلك إضافة قسم خاص بالخصائص الفيزيائية والكيميائية لهذه الهلاميات، مع التركيز على التوصيف المورفولوجي، ودراسات امتصاص الماء، والخصائص الميكانيكية للمواد.

بعد ذلك، بدأت المناقشة حول المزيد من التطبيقات، ومن بين هذه التطبيقات، تم استخدامها في الأجهزة الطبية الحيوية التي تستخدم للشفاء مثل التئام الجروح، والهندسة النسيجية، ونقل الأدوية، والاستشعار الحيوي المحضر للاستشعار الحيوي. تم التركيز بشكل خاص على تلك الآليات التفاعلية بين مجموعات قاعدة شيف ومركب الثيادايازول والنظم البيولوجية التي تحقق آلية الشفاء للهلاميات المائية والتي تلعب دورًا حاسمًا في آلية الشفاء للهلاميات المائية.

علاوة على ذلك، تتناول المراجعة العلمية المذكورة القضايا والعقبات المتعلقة بهذه المواد وتقدم أحكامًا دقيقة حول الحاضر والمستقبل لهذا المجال. تقدم هذه المراجعة والتقييم الجاد نظرة عميقة على التأثيرات التحويلية للهلاميات المائية المعدلة بقواعد شيف ومركبات الثيادايازول عبر المجال الطبي الحيوي بالكامل. يتم تحقيق نهج جديد من خلال هذه المراجعة، حيث يتم توعية الجمهورمن خلال تقديم أحدث الاكتشافات المتعلقة بإمكانية الهلاميات المائية المعدلة بقواعد شيف ومركبات الثيادايازول في تحقيق تطبيقات طبية حيوية مبتكرة.

1. Introduction:

The Schiff base is a significant compound of coordination chemistry, and it is the part of the field that has attracted much attention in the last few years. It can make hydrogels when installed. Even though the handling of Schiff bases and hydrogels is different, they both are more efficient and have dense internal structures. (1) The Schiff base is reversible. It can react even in mild conditions, whereas the hydrogels can heal spontaneously after damage, consequently enabling them to recover their structures and functions. Hence, the materials are called self-healing hydrogels [1].

2. Hydrogels:

According to the International Union of Pure and Applied Chemistry (IUPAC), hydrogels are polymer networks or network components of a colloidal network known as aqua gels [2]. The term 'aqua gel' is simply a water-based material that forms a gel on account of this. Understanding this definition is crucial to recognizing the unique features hydrogels have [3]. The entire concept of a hydrogel is that it has a unique structure consisting of a solid matrix full of interconnected porosities. A minimum of at least 10% of the volume comes from interstitial fluid, and water is mainly used, but there can also be some other types of fluids [4] The combination of porous, permeable solids and interstitial fluid gives hydrogels unique properties that stand out and make them applicable in different sectors [4] This composition is truly remarkable in materials research and technology. A hydrogel has crosslinks that hold the polymers together and can fall under the chemical and physical types[5,6] In particular, chemical hydrogels pull through with the help of covalent crosslinking bonds, while physical hydrogels have minimal ownership, primarily non-covalent bonds [7] The third component, namely, the porous and permeable solids of hydrogels, play a vital role in the formation of a more solid 3D structure as they constitute a network of natural or synthetic polymers like polyethylene glycol or polyacrylamide and a fluid-insoluble in water necessary for the needed support and structure [8] This interjection will enable listeners to better understand the constituents in hydrogels, for instance, the components' capability to absorb the sheer amounts of water or biofluids [9] The financing of massive projects, particularly in biomedical applications, is premised on these properties being essential, underscoring the crucial role of hydrogels in this field. [10].

3. Preparation:

Different polymeric materials, such as natural or synthetic polymers, are used in the preparation of hydrogels. Hyaluronic acid, chitosan, heparin, alginate, gelatin, and fibrin are all natural polymers used to make hydrogels [11].

When contrasting typical synthetic polymers with natural hydrogels, the latter typically exhibit non-toxic properties and offer numerous advantages for medical applications, including antibiotic/antifungal effects and the promotion of Tissue regeneration that is nearby. However, their stability and strength generally fall below that of synthetic hydrogels [12] Polyvinyl alcohol, polyethylene glycol, sodium polyacrylate, acrylate polymers, and copolymers are among the commonly used synthetic polymers, and they are capable of becoming toxic when heated [9].

4. Classification of hydrogel products:

The classification of hydrogel products is determined by their source and polymeric composition. The hydrogel source can be classified into two groups based on their natural or synthetic origins [13] While the polymeric composition can be exemplified in three states:

4.1 Homopolymeric hydrogels:

A single monomer forms a polymeric network that constitutes a basic structural unit [14] The cross-linking of the skeletal structure of these polymers is

determined by the monomer and polymerization technique.

4.2 Copolymer hydrogels:

The composition comprises a hydrophilic component composed of two or more distinct monomers that are arranged in a random block or alternating pattern across the polymeric chain [15].

4.3 Multipolymer Hydrogels:

An interpenetrating polymeric hydrogel is a significant group within this category of polymers, which consists of two independent synthetic polymer components (cross-linked polymer) or interconnected natural polymer components (non-cross-linked polymer [16,17].

The polymers crosslink by using small molecules. Covalently cross-linked polymers exhibit enhanced mechanical strength in comparison to physically cross-linked polymers. To obviate the requirement for crosslinking agents, polymers have been modified with specific reactive functional groups to facilitate the in-situ synthesis of hydrogels. Various hydrogels have been successfully developed based on the judicious selection of functional groups, as detailed in Table 1. [18].

Copolymers are used to graft many hydrophilic monomers. An example is acrylamide, which has been used with starch to prepare fast-absorbing hydrogels.

This method includes hydrolysis of the starch flavour with polyacrylonitrile, where mixing starch with water and grafting with acrylonitrile is the main process in this experiment. Subsequently, the separation and drying process takes place, which is followed by saponification with alkali at a temperature of 95 degrees Celsius for an hour.

After that, precipitation is done after methanol and water-free ethanol treatment. To reach the drying process under vacuum at a temperature of 60 degrees Celsius for 3 hours.

In the end, we use the redox system (Fe^{2+}/H_2O_2) as a source [$OH^{\cdot}$] of free radicals [19]. Furthermore, the preparation of super-absorbent hydrogels involves the use of acrylic acid (AA) and acrylonitrile (AN) in starch. Figure 1 shows the process of designing and preparing a grafting hydrogel using starch [20].

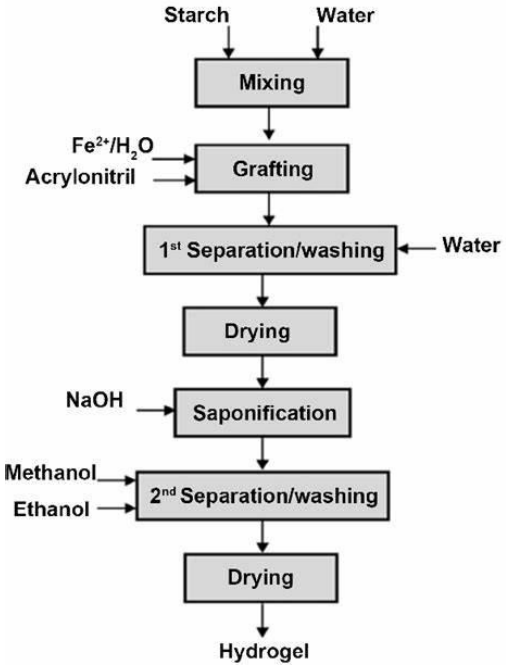
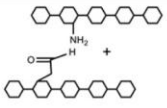
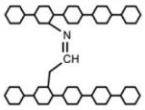
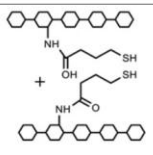
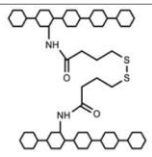
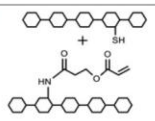
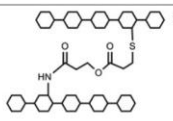


Figure (1): The block diagram outlines the process for preparing a high-swelling material.

Table (1): Crosslinking of polymers through reactive functional groups [21-22].

Reaction	Reaction Conditions	Reactive Polymer Groups	Crosslinkage	Comments
Schiff base mechanism	Neutral pH			Good candidate for in situ gel formation. Reaction takes minimum 10 min.
Disulfide bonding	Neutral pH			Good candidate for in situ gel formation and hydrogels have good mucoadhesivity.
Michael addition	Weak base and in presence of catalyst			Good candidate for in situ gel formation and hydrogels have good mucoadhesivity.

5. Hydrogel technical features:

Hydrogel cannot always be highly efficient. As a result, production reaction variables must be tuned to attain the desired balance of attributes. Healthy gel products must have the highest absorption and lowest re-wetting rates. The hydrogels used in drug delivery must be porous and respond to either temperature or pH.

The functional features of hydrogel materials include:

- High absorption capacity in saline
- The desired rate of absorption based on application requirements
- High absorbency under load
- Low soluble content and residual monomer
- Competitive price
- Stability and durability during storage and in an environment that swells
- Biodegradability without the formation of toxic species
- pH neutrality after swelling in water
- Colorlessness, odorlessness, and non-toxic nature
- Photostability

- Re-wetting capability if required for specific applications, such as in agriculture or hygiene Additionally, hydrogels can be classified based on ionic charge as cationic, anionic, and neutral hydrogels, where the charge on the overall network depends on the charge on the polymer. Figure 2 provides a visual representation of the hydrogel's classification.

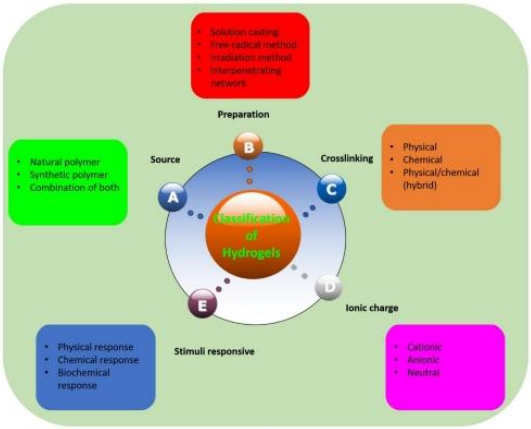


Figure (2): Describes the classification of hydrogels**.**

6. Hydrogels Based on Schiff Base

The preparation of hydrogels can be summarized based on the types of different Schiff bases associated with them. Schiff bases are important interactions in coordination chemistry and have recently received great interest in the formation of self-healing hydrogels [23].

Schiff bases demonstrate reversibility even under mild conditions, facilitating the recovery of hydrogels' structure and functionality following damage [24]. The pH sensitivity of Schiff bases confers responsiveness to biologically relevant stimuli in hydrogels [25] Diverse Schiff bases can impart tunable mechanical properties and chemical stability to hydrogels [26].

There are many applications for hydrogels, including drug delivery [24,25]., wound healing [25,26], tissue regeneration [27,28], many biomedical applications [29], tissue adhesives [30], and biosensors [31].

The use of hydrogels with Schiff base connections in several biomedical fields is illustrated in Figure 3.

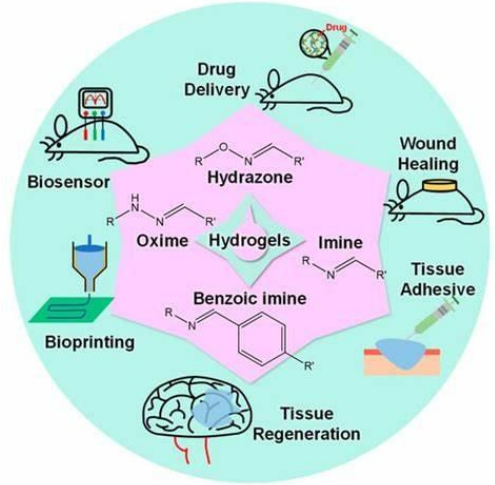


Figure (3): biomedical application for hydrogels based on Schiff base

Reactive requirements include covalent bonds between the mono- or di-amine groups with the aldehyde group [32]. These elements are used to create hydrogel networks by interacting Schiff requirements with cells, tissues and biological molecules in physiological requirements. Therefore, using these dynamically cross-linked networks gives the gels self-healing properties [33]. According to its chemical structure, the Schiff base is pH-responsive[34,35].

Hydrogels are characterized as three-dimensional chemical compounds due to their high-water content, placing them within the significant category of soft materials [36,37]. Physiologically, hydrogels resemble cell growth. One of its most important uses is to imitate the extracellular matrix [38].

The interaction and remodeling of these cells with the extracellular matrix (ECM) are essential for regulating various cellular behaviors, such as proliferation [39], differentiation [40], and migration [41]. This is key to the development of hydrogels for many biomedical applications [42]. such as tissue engineering [43], wound healing [44] and drug delivery [45].

7. 1, 3, 4-Thiadiazole

1, 3, 4-Thiadiazole, is extensively utilized by scientific chemist researchers [46,47].1, 3, 4 thiadiazole is an important heterocyclic nucleus that possesses various biological activities such as anti-inflammatory, and antimicrobial.

Thiadiazole is a small molecule of heterocyclic ring integrated with nitrogen and sulphur. Thiadiazole [48,49] and triazole [50,51] have been extensively studied based on their synthetic and biological applications. Thiazole is the most commonly reported compound in literature. It is a 5-—to 5-membered ring moiety containing nitrogen and sulphur at positions 1 and 3, respectively.

1, 3, 4 thiadiazole were considered the heterocyclic compounds and most significant in various biological activities.

In recent years, there has been a growing interest in the study of substituted 1,3,4-thiadiazole derivatives due to their diverse pharmacological properties. Figure 4 illustrates 1,3,4-thiadiazole derivatives 20, 21, 22, 23, and 24 as potential anti-diabetic agents [52].

The thiadiazole molecule can exist in four different structures: 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-thiadiazole, and 1,2,4-thiadiazole. Among these, 1,3,4-thiadiazole demonstrates significant versatility due to its pharmacological and biological activities, as depicted in Figure 5 [52].

Heterocyclic molecules are cyclic compounds that contain carbon as well as other elements such as oxygen, nitrogen, and sulfur. [53] Examples of heterocyclic molecules containing a single heteroatom include pyrrole, furan, and thiophene. On the other hand, heterocyclic molecules consisting of more than one heteroatom include azole, pyrrole, thiazole, thiadiazole, oxadiazole, and triazene [53].

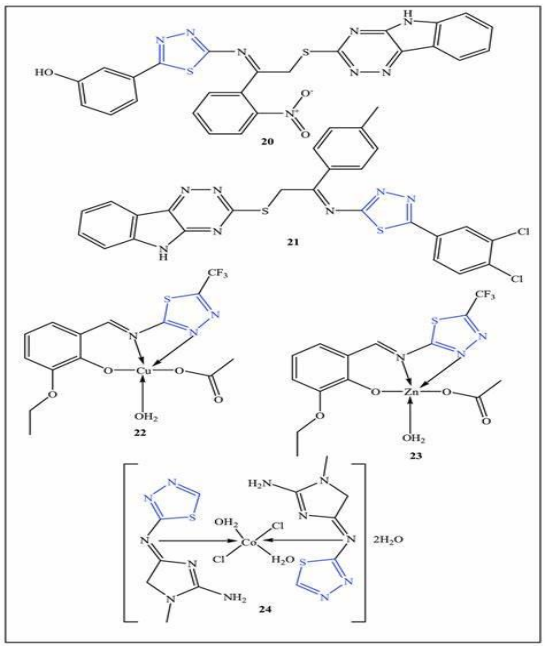


Figure (4): Compounds 20, 21, 22, 23, and 24, which are derivatives of 1, 3, 4-thiadiazole, have shown potential as effective agents for managing diabetes.

Figure (5): Thiadiazole isomers

8. Conclusions:

The incorporation of Schiff-base thiadiazole-modified hydrogels demonstrates a significant leap forward in the realm of biomedical materials because of their distinctive amalgamation of high-water content, biocompatibility, and adjustable mechanical attributes. The amalgamation of Schiff-base and thiadiazole entities has conferred these hydrogels with enhanced functionalities, including exceptional antimicrobial properties, improved drug delivery capabilities, and robust bio-adhesive characteristics. This comprehensive review has meticulously examined the synthesis methodologies, physicochemical properties, and diverse biomedical applications of these innovative hydrogels, encompassing their contributions to wound healing, tissue engineering, drug delivery, and biosensing. Despite the considerable progress achieved, challenges persist in fine-tuning these materials for clinical use, specifically in their stability, safety, and large-scale production. Nonetheless, the potential for Schiff-base thiadiazole-modified hydrogels to transform numerous biomedical applications is unmistakable, and forthcoming research endeavours are poised to investigate further and enhance these pioneering materials for broader medical integration.

9. Acknowledgment

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