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Review

Recent advances in smart hydrogels for biomedical applications: From self-assembly to functional approaches

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ABSTRACT

This review discusses basic aspects used to control the architecture and functional properties of smart hydrogels. The introduction briefly outlines what has been accomplished regarding smart hydrogels and explores historical aspects and the fundamental understanding of these systems. Then, a short discussion on the chemical interactions and the main variables involved in architectural construction is exhibited. Further analysis provides the basis for optimizing biological responses through system modulation. Finally, we outline perspectives and challenges for building smart hydrogels into functionalized and modulated delivery systems.

1. Introduction

The development of hydrogels as functional biomaterials has revolutionized the field of study concerning responsive materials. Initially, hydrogels were developed for biomedical applications, especially tissue scaffolds and contact lenses [1]. In the late 19th century, hydrogels were first described as colloidal gels from inorganic salt. Around the middle of the 20th century, Wichterle and Lim termed them as water-swollen crosslinked polymeric network(s) [2,3]. Currently, hydrogels can be defined as three-dimensional networks of hydrophilic polymers. These systems have the ability to swell and absorb large amounts of water or biological fluids without losing their structure [4–6]. Their capacity to absorb liquid is due the presence of hydrophilic compounds attached to the polymer chains, such as amid, amino, carboxyl and hydroxyl groups, which are able to ionize in the presence of water. Furthermore, their physical properties, such as swelling, surface characteristics and mechanical strength, can be modulated by physico-chemical reactions to improve elasticity and mechanical resistance, which are important features to considered when developing delivery systems [3,7,8].

The most common terms associated with hydrogels are: ocular lens, wound healing [9], super-absorbents [10], tissue engineering, tissue scaffolds, cell immobilization [11] and drug delivery systems [12]. The number of publications reported in the Science Direct database involving hydrogels, containing such keywords, over the last ten years showed exponential growth, including books, journal articles and reference works (Fig. 1). Although this popularity can be observed for all aforementioned subjects, tissue engineering and drug delivery standout since they represent the majority of the publications. Remarkable, nonetheless, is the similar increase of studies regarding tissue scaffolds, tissue engineering, wound healing and drug delivery.

Since 2000, the number of publications involving the term 'hydrogels' expanded notably [13]. In parallel, the wide applicability of hydrogel as functional materials has attracted great interest among researchers and several industry segments [14].

Unlike conventional hydrogels, which exhibit swelling/deswelling properties linked to water availability, smart or stimulus-responsive hydrogels are the most promising materials because of their additional properties. These types of hydrogels are most often related to the physical, chemical and biological fields [13,15,16] and their unique properties can be associated with environmental factors, such as external stimuli that promotes a change in organization.

Although the first studies related to hydrogels appeared in 1894, the word "smart" was introduced in 1948 by Kuhn and co-workers [17]. This most recent nomenclature gained importance because they are capable of exploitation based on specific triggers (stimuli) to induce changes in structure and function [3]. The first publication reported was on poly(acrylic acid) polymer molecules that could undergo structural adjustments according to the media pH [18]. At the same time, publications reported such profiles for different polymeric networks including the pioneering smart hydrogels [18–21]. This drug delivery concept is denominated as "smart" because it can detect prevailing stimuli and respond through structural, morphological or functional changes resulting in the release of entrapped drugs in a controlled manner [22].

A set of criteria has been used to classify these systems, including

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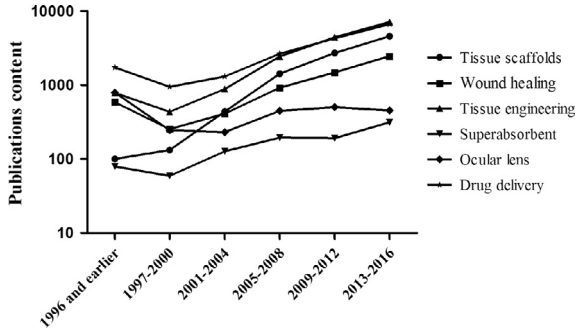

Fig. 1. Summary of the content found related to common terms in the Science Direct database. Publications include journal articles, books and reference works. Research conducted in September 2017.

origin (natural or synthetic), degradability and cross-linking mechanisms for self-assembly. Chemically cross-linked hydrogel networks are generated by covalent bounds between polymer chains resulting in permanent junctions [3]. On the other hand, physically cross-linked structures are designed through supramolecular forces (noncovalent) forming rapid and reversible networks, a feature that we are particularly interested in [2]. Smart hydrogels can be classified by several criteria. Publications focused on drug delivery have primarily considered external types of stimuli. Responses can be induced by physical or chemical stimuli. The first type includes: pressure, light, temperature, and magnetic or electric fields. Chemical or biochemical stimuli include ionic strength, pH and ions. Complementing these factors, punctual molecular events, chemical or biological species availability can also be explored [7,8,13]. Moreover, these systems can be designed to respond a multiple stimuli listed above [21].

Many reviews have been reported to introduce the field of stimuli responsive hydrogel systems, although a large portion of these publications focused only on applications. The present review focuses on the basic concepts and responsivity mechanisms guided by dynamic interactions that provide valuable tools for designing smart hydrogels for functional approaches.

2. Self-assembly for designing smart hydrogels

Supramolecular chemistry is defined as the chemistry beyond the molecule. This field has evolved by engaging the fundamental and applied aspects of supramolecular interaction manipulation [23,24]. Although a major focus has been on physical interactions (e.g., hydrophobic, hydrogen bond and electrostatics), the dynamic nature of supramolecular chemistry makes it applicable to the development of smart hydrogels. In this sense, not only non-covalent links but also dynamic covalent bonds can be explored in tailoring stimuli-responsiveness [25–27]. Smart hydrogels might self-assemble by establishing supramolecular interactions such as ionic bonds, weak physical entanglements, and hydrogen bonds. However, covalent chemical links may also be used to obtain the same results [28]. The self-assembly of highly organized macromolecular systems nanostructured by dynamic interactions has been strongly explored in drug delivery systems [2].

Their dynamic nature is an essential feature for the practical design of responsive systems. Therefore, it is mandatory to understand the concept of the dynamics in order to associate its meaning with hydrogels categorized as “smart”. The static behavior of conventional hydrogels *versus* the dynamic behavior of smart hydrogels are two extremes of behavior that can significantly affect the performance of drug delivery systems (Fig. 2). This paradigm shift that contrasts the static and dynamic nature of materials has been clearly identified in hydrogel designs. Thus, traditional static hydrogels designed as bioinert materials have been replaced by dynamic systems that incorporate sophisticated functions [29,30].

The physicochemistry behind the supramolecular interactions and the dynamic covalent bonds are of primary importance to the synthesis steps and performance of biological systems. By manipulating the factors involved in these links, we control the structural properties of the final system. In this context, many supramolecular and dynamic covalent bonds have been explored through the advent of smart hydrogels, as summarized in Table 1.

The development of hydrogels based on supramolecular and dynamic covalent chemistry enables the biological functions that are impossible to achieve by static links. The modulation of drug release from delivery systems, self-healing and tissue adhesiveness are some of the interesting functions that can be tailored by controlling the system properties during the synthesis procedure [39,40]. The dynamics of smart hydrogels can be designed to respond to a physical, chemical or biological stimulus. Upon receiving these external inputs, the hydrogel undergoes a structural/morphological property change, which leads to the desired outcomes. This off-on transition is ultimately responsible for achieving the biological function. Expected responses can be manifold and include degradation, drug release, swelling, changes in shape or surface, conformational modifications or micellization [41].

The final morphology expected for the hydrogel is associated with a series of variables, which primarily includes the synthesis or treatment procedures of the original polymer, monomer composition and their ratios, and the crosslinking method [42].

Polymer science and drug delivery together represent most of the active branches in the development of therapeutics [43]. In drug delivery systems, pharmaceutically active compounds are loaded into a hydrogel, which is then administered to the body where the drugs are released in a sustained manner for periods ranging from several days to several months. Furthermore, introduction or association of the drug to the polymeric pattern can provide a passive function as a drug carrier, alter the degradation process, or minimize immunogenicity and toxicity, in addition to possibly increasing circulation time [41]. Therefore, the frequency of drug administration can be decreased and peak concentrations can be avoided, reducing potentially harmful side effects. Alternatively, hydrogels are used specifically to deliver its content to the target area. Therefore, the hydrogel structure might protect drugs from hostile environments and control drug release by changing the gel structure in response to environmental stimuli.

To further reflect on these systems, the following section will outline different classes of smart hydrogels and their specific features, including functional groups and factors involved in responsiveness. Furthermore, selected comprehensible examples in drug delivery will be given, and, to conclude, a brief outlook of future perspectives will be addressed.

2.1. Thermo-responsive hydrogels

Thermo-responsive hydrogels are one of the most studied classes of stimuli systems in tissue engineering and drug delivery research, as medium temperature may fluctuate in physiological and pathological conditions. These hydrogels, composed mainly of natural and synthetic polymers with balanced hydrophilic and hydrophobic groups in their chains (Table 2) are characterized by their ability to undergo reversible modifications as volume changes. They also swell or de-swell in response to a critical temperature, which causes a sudden change in the solvation of their molecules, conformational state and, consequently, water-solubility [41,44–47].

Thermo-responsive hydrogels can be divided into two groups according to their behavior with the surrounding solvent molecules. Extensively studied, lower critical solution temperature (LCST) hydrogels exhibit non-linear responses, where the polymer’s solubility decreases as the temperature increases, leading to the formation of a more structures gel. The second type, upper critical solution temperature (UCST) systems, on the other hand, become soluble upon heating.

For the LCTS hydrogels, at lower temperatures, the water molecules are arranged around the polymer, establishing hydrogen-bonds with the