



Review

Hydrogels in a historical perspective: From simple networks to smart materials



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ABSTRACT

Over the past decades, significant progress has been made in the field of hydrogels as functional biomaterials. Bio-medical application of hydrogels was initially hindered by the toxicity of crosslinking agents and limitations of hydrogel formation under physiological conditions. Emerging knowledge in polymer chemistry and increased understanding of biological processes resulted in the design of versatile materials and minimally invasive therapies. Hydrogel matrices comprise a wide range of natural and synthetic polymers held together by a variety of physical or chemical crosslinks. With their capacity to embed pharmaceutical agents in their hydrophilic crosslinked network, hydrogels form promising materials for controlled drug release and tissue engineering. Despite all their beneficial properties, there are still several challenges to overcome for clinical translation. In this review, we provide a historical overview of the developments in hydrogel research from simple networks to smart materials.

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1. Introduction

Hydrogels are three-dimensional polymer networks that are able to retain a large amount of water in their swollen state [1]. Hydrogels may be classified as natural, synthetic or hybrid, depending on the source of the constituting polymers. Hydrogels can be chemically crosslinked by covalent bonds, physically crosslinked by non-covalent interactions or crosslinked by a combination of both. The interactions responsible for the water sorption include capillary, osmotic and hydration forces, which are counterbalanced by the forces exerted by the crosslinked polymer chains in resisting expansion [2]. The equilibrium swollen state depends on the magnitudes of these opposing effects, and determines to a large extent some important properties of the hydrogel, including internal transport and diffusion characteristics, and mechanical strength. Many of these properties are governed not only by the degree of swelling, but also directly by the chemical nature of the polymer network and the network morphology. Due to their high water content, the properties of hydrogels resemble those of biological tissues, resulting in an excellent biocompatibility. Furthermore, their soft and rubbery nature minimizes inflammatory reactions of the surrounding cells [3]. After their discovery in the 1960s by Wichterle and Lim [4] hydrogels were first successfully applied as contact lenses. Later, hydrogels have been frequently used as systems for the controlled delivery of biologically active agents. These hydrogels facilitate the localized and sustained release of a drug, thereby decreasing the number of administrations, preventing damage to the drug and allowing for relatively low doses. In this field, the Journal of Controlled Release has played a major role since its launch in 1984 as a place to publish state-of-the-art research and review articles concerning drug delivery from hydrogels. In this contribution for the 30th Anniversary Issue of the Journal of Controlled Release, we present a historical overview of the major developments in hydrogel research over the last 50 years, starting with the relatively simple, chemically crosslinked networks of the 1960s and concluding with today's 'smart' hydrogels (Fig. 1). We particularly focus on hydrogels for controlled drug delivery, but we also briefly address hydrogels for other biomedical applications such as tissue engineering. Lastly, we present our view on the future of hydrogel research.

Because of the vastness of this research field, obviously not all contributions of the last 50 years could be included in this historical overview. However, many excellent reviews exist that focus on specific areas in hydrogel research [5–14].

2. First generation hydrogels

Around 1900, the term 'hydrogel' first appeared in scientific literature when it was used to describe a colloidal gel of inorganic salts [15]. In 1960, Wichterle and Lim were the first to report on hydrogels as we know them nowadays, e.g. as water-swollen crosslinked macromolecular networks, in their landmark paper about poly(2-hydroxyethyl methacrylate) (pHEMA) gels for use as soft contact lenses [4]. In the two decades following this discovery, hydrogel research remained essentially focused on relatively simple, chemically crosslinked networks of synthetic polymers with applications mainly in ophthalmic and drug delivery research. The straightforward network structure was also well-suited for fundamental

characterization and modeling of various physico-chemical hydrogel properties such as solute diffusivity and crosslink density. Hydrogels were mainly prepared either by polymerization of water-soluble monomers in the presence of a multifunctional crosslinker or by crosslinking of hydrophilic polymers (Fig. 2). These categories among the first generation of hydrogels will be discussed separately hereafter including the most representative examples. The chemical structures of the polymers that were applied most frequently in hydrogels, pHEMA, poly(vinyl alcohol) (PVA) and poly(ethylene glycol) (PEG), are shown in Fig. 3.

2.1. Hydrogels prepared by polymerization of water-soluble monomers

The hydrogels in this category are prepared by chain-addition reactions, mostly employing vinyl monomers. The mechanism of this type of polymerization has been well established [16] and, in short, consists of an initiating free radical species which adds to a vinyl monomer molecule by opening the π -bond to form a new radical, until the polymerization is terminated at some point by recombination of two radical species or disproportionation. The polymerization of a monomer in the presence of a crosslinking agent in solution has various advantageous aspects over bulk polymerization, such as rapid hydrogel formation under mild conditions and the possibility to obtain pre-defined shapes because the starting materials are in the liquid form [17].

An important hydrogel-forming polymer in terms of production volume in this category is poly(acrylamide) (PAM), which was initially employed mainly in industrial applications such as agricultural gels. In the 1960s, PAM hydrogels were also used for the physical entrapment

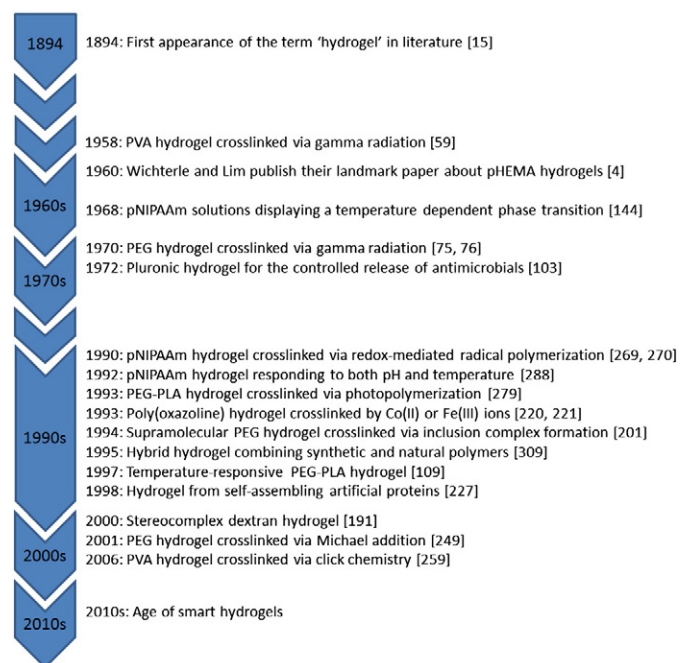


Fig. 1. Timeline presenting the most important events in the history of hydrogel research.

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