Available online at www.sciencedirect.com
ScienceDirect
Biomaterials 28 (2007) 5185–5192
Biomaterials
www.elsevier.com/locate/biomaterials

Leading Opinion

Hydrogel biomaterials: A smart future?☆

Jindřich Kopeček[a,b,*]

[a]Department of Bioengineering, University of Utah, Salt Lake City, UT 84112, USA
[b]Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, UT 84112, USA

Received 8 May 2007; accepted 17 July 2007
Available online 13 August 2007

Abstract

Hydrogels were the first biomaterials developed for human use. The state-of-the-art and potential for the future are discussed. Recently, new designs have produced mechanically strong synthetic hydrogels. Protein-based hydrogels and hybrid hydrogels containing protein domains present a novel advance; such biomaterials may self-assemble from block or graft copolymers containing biorecognition domains. One of the domains, the coiled coil, ubiquitously found in nature, has been used as an example to demonstrate the developments in the design of smart hydrogels. The application potential of synthetic, protein based, DNA based, and hybrid hydrogels bodes well for the future of this class of biomaterials.

Keywords: Hydrogels; Smart biomaterials; Self-assembly; Hybrid biomaterials; Bionanotechnology

1. Introduction

Hydrogels are water-swollen polymeric materials that maintain a distinct three-dimensional structure. They were the first biomaterials designed for use in the human body [1,2]. Traditional methods of biomaterials synthesis include crosslinking copolymerization, crosslinking of reactive polymer precursors, and crosslinking via polymer–polymer reaction. These methods of hydrogel synthesis were limited in the control of their detailed structure, due to side reactions the networks contain cycles, unreacted pendant groups, and entanglements. Other inadequacies of traditional hydrogels have been poor mechanical properties and slow or delayed response times to external stimuli [2].

Novel approaches in hydrogel design have revitalized this field of biomaterials research. New ideas on the design of hydrogels with substantially enhanced mechanical properties [3–6], superporous [7] and comb-type grafted hydrogels [8] with fast response times, self-assembling hydrogels from hybrid graft copolymers with property-controlling protein domains [9,10], and from genetically engineered triblock copolymers [11,12] are just a few examples of hydrogel biomaterials with a smart future.

What are the limitations for further developments of the basic science and in the applications of hydrogels? Let us discuss individual groups of hydrogels and point out the possibilities for their development into intelligent materials with applications in therapeutics, sensors, microfluidic systems, nanoreactors, and interactive surfaces.

2. Synthetic (traditional) hydrogels

Traditional synthetic methods have produced numerous hydrogel materials with excellent properties, e.g. hydrogel implants [13] and soft contact lenses [14]. Previously, these synthetic pathways did not permit an exact control of chain length, sequence, and three-dimensional structure. Developments in controlled radical polymerization, such as atom transfer radical polymerization (ATRP), reversible addition-fragmentation chain transfer (RAFT) polymerization, and nitroxide-mediated polymerization [15] have provided

☆ *Note*: Leading Opinions: This paper provides evidence-based scientific opinions on topical and important issues in biomaterials science. They have some features of an invited editorial but are based on scientific facts, and some features of a review paper, without attempting to be comprehensive. These papers have been reviewed for factual, scientific content.

*Corresponding author at: Department of Bioengineering, University of Utah, Salt Lake City, UT 84112, USA.
E-mail address: jindrich.kopecek@utah.edu

0142-9612/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.biomaterials.2007.07.044

the potential to produce macromolecules with a narrow molecular weight distribution. New catalysts (transition metal complexes) and novel experimental approaches (polymerization under vacuum or at low temperature) afford control of the polymerization of α-amino acid *N*-carboxyanhydrides and permit the production of well-defined synthetic polypeptides [16].

2.1. Hydrogels with excellent mechanical properties

Recently, there have been several important developments, which have broadened the applicability of hydrogel materials. Three main approaches, namely introduction of sliding crosslinking agents [3], double network hydrogels [4], and nanocomposite (clay filled) hydrogels [5] have markedly improved the mechanical properties of hydrogels (Fig. 1).

A new concept of chain crosslinking–sliding crosslinking agents—was introduced by Okumura and Ito [3]. By chemically crosslinking two cyclodextrin molecules, each threaded on a different PEG chain (end-capped with a bulky group, such as adamantan), a sliding double ring crosslinking agent was produced. This resulted in outstanding mechanical properties—a high degree of swelling in water and a high stretching ratio without fracture. The sliding crosslinks in these so-called topological gels apparently equalized the tension along the polymer chains (“pulley effect”) [3].

Double networks (DN) are a subset of interpenetrating networks (IPNs) formed by two hydrophilic networks, one highly crosslinked, the other loosely crosslinked [4]. For example, a DN composed of two mechanically weak hydrophilic networks, poly(2-acrylamido-2-methylpropanesulfonic acid) and polyacrylamide, provides a hydrogel with outstanding mechanical properties. Hydrogels containing about 90% water possessed an elastic modulus of 0.3 MPa and fracture stress of ~10 MPa, demonstrating both hardness and toughness. This was explained by effective relaxation of locally applied stress and dissipation of crack energy through combination of the different structures and densities of the two networks [4].

Nanocomposite (clay filled) hydrogels are organic–inorganic hybrids. They are based on *N*-isopropylacrylamide (NIPAAm) with hectorite, $[Mg_{5.34}Li_{0.66}Si_8O_{20}(OH)_4]Na_{0.66}$, as multifunctional crosslinker [5]. Exfoliated clay platelets are uniformly dispersed in an aqueous medium containing the NIPAAm monomer; polyNIPAAm chains are grafted on the clay surface by one or two ends. Here, up to 1500% elongation-at-break values were obtained. It is interesting to note that mechanically robust hydrogels could only be prepared by radical polymerization of NIPAAm in the presence of clay. Mixing of polyNIPAAm with clay did not produce homogeneous hydrogels with robust mechanical properties. These hydrogels possessed extremely high surface hydrophobicities, as demonstrated by contact angle measurements. The main contributing factor was likely the alignment of *N*-isopropyl groups at the gel–air interface [6].

3. Stimuli-sensitive hydrogels

Some hydrogels undergo continuous or discontinuous changes in swelling that are mediated by external stimuli such as changes in pH, temperature, ionic strength, solvent type, electric and magnetic fields, light, and the presence of chelating species. The majority of stimuli responsive hydrogels were created using conventional (traditional) methods of synthesis of a relatively small number of synthetic polymers, especially (meth)acrylate derivatives and their copolymers. In 1968, Dušek and Patterson [17] theoretically predicted that changes in external conditions might result in abrupt changes of the hydrogel’s degree of swelling (phase transition). Indeed, 10 years later, Tanaka [18] and others [19] have verified the theory by experimental observations.

Lately, numerous polypeptide based responsive hydrogels have been designed, synthesized, and evaluated. These include hydrogels formed from block copolypeptides [20],

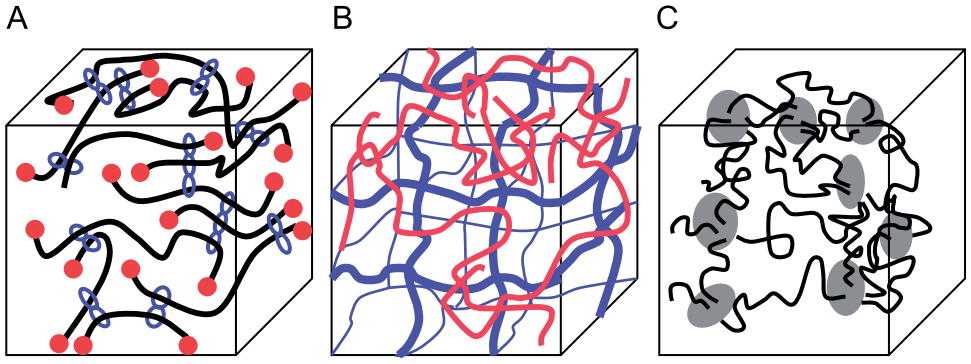

Fig. 1. Synthetic hydrogels with excellent mechanical properties. (A) Topological sliding hydrogel. α-Cyclodextrin moieties threaded on PEG chains, end-capped with a bulky group, are crosslinked by trichlorotriazine producing double ring crosslinks freely movable along the PEG chains (adapted from Ref. [3]); (B) double network hydrogels composed from two hydrophilic networks, one highly crosslinked, the other loosely crosslinked [4]; and (C) nanocomposite (clay filled) hydrogels synthesized by radical polymerization of *N*-isopropylacrylamide in the presence of uniformly dispersed clay sheets (adapted from Ref. [5]).