European Polymer Journal 93 (2017) 642–669

Contents lists available at ScienceDirect

European Polymer Journal

journal homepage: www.elsevier.com/locate/europolj

Feature Article - Review

Reversible interactions in self-healing and shape memory hydrogels

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ARTICLE INFO

Keywords:
Self-healing
Shape memory
Hydrogels
Structure-property correlations

ABSTRACT

Responsive hydrogels have been extensively studied in the past decades because they are able to interact with their biological environment in a pre-programmed manner. Several biomedical applications have already been achieved (or at least approached) by *in vivo* experiments. As a class, injectable hydrogels gained considerable attention because of their minimally invasive implantation. However, the final shaping of hydrogel implants is not resolved, and their lifetime is limited because of their insufficient mechanical stability. The solution to these challenges can be given by two seemingly independent properties, shape memory and self-healing. Both properties are well-known for conventional polymers but research on the shape memory or self-healing of hydrogels is in its infancy. In this study, we introduce the molecular mechanisms behind these two properties with a focus on hydrogels, attempt to provide a general overview on the role of reversible physical and chemical interactions, and discuss the similarities between the background of shape memory and self-healing. There are a number of open questions regarding the uniform characterisation of such hydrogels, and their theoretical description is very incomplete, but the developed systems hold great promise for future applications. In the final part of the paper, we note that the synthesis of hydrogels providing both self-healing and shape memory is a difficult challenge, but some examples do exist. Future research in these fields should focus on a better understanding of structure-property correlations and should uncover additional fields of application for these advanced materials.

1. Introduction

Polymeric hydrogels are three-dimensional hydrophilic networks consisting of cross-linked macromolecules and a substantial amount of absorbed water. The extensive research on hydrogels is motivated by the versatile and tailor-made properties of such materials and their similarity to body tissues, which allows various uses in medical applications e.g., wound dressing, controlled/targeted delivery of bioactive compounds and tissue regeneration. Their most relevant properties are biocompatibility, controlled (bio)degradability, low surface friction, ability to encapsulate drug molecules, gene sequences or cells, adequate morphology for cell proliferation and stimuli-responsive characteristics. The stimuli-responsiveness of hydrogels or, in other words, their programmable response to external signals, is a key issue in biological applications; thus, the spatial and/or temporal control of their properties by well-defined physical and chemical stimuli is studied by an immense number of researchers [1–11].

Aside from the attractive properties of hydrogels, less attention has been paid to a few of their adverse characteristics. Medical implants that are made of conventional materials, e.g., ceramics or metals, are usually mechanically stable and, thus, their performance does not deteriorate over time. In contrast, hydrogels generally show poor mechanical properties, and the development of

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http://dx.doi.org/10.1016/j.eurpolymj.2017.05.020
Received 1 March 2017; Received in revised form 11 May 2017; Accepted 13 May 2017
Available online 17 May 2017
0014-3057/

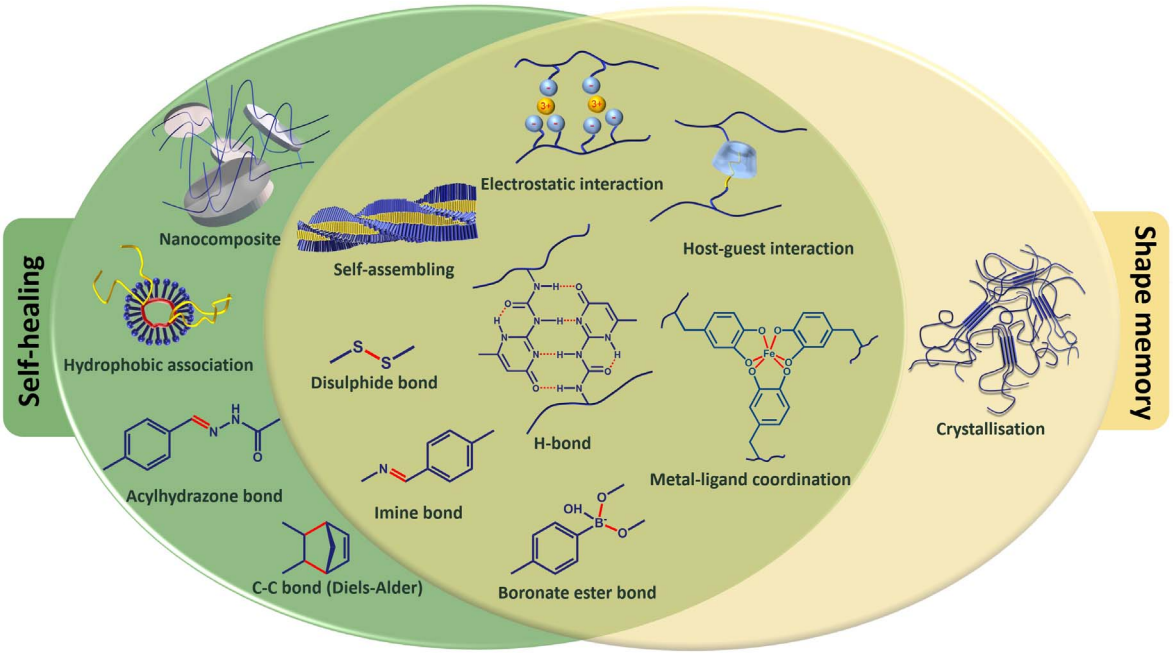

Fig. 1. The most important interactions employed to construct self-healing and/or shape memory hydrogels.

mechanical damages and cracks within the physiological environment does not allow them to perform their function over a long time period. Consequently, to exploit the full potential of hydrogel formulations, self-healing is strongly needed to enable them to restore their function after mechanical damage, similar to wound-healing in the living body. The healing of hydrogels should be based on relatively simple chemical or physical interactions and should require fast, efficient and autonomous re-formation of their structure [4,9,12–14].

The discussion of self-healing leads us to a seemingly different property: the externally controlled, non-isotropic response of hydrogels, which is referred to as shape memory [15,16]. The application of shape memory in hydrogels is in its infancy, but we expect its use to widen shortly because there is a natural need to change the shape of the implanted hydrogel at the site of action depending on the application. Injectable hydrogels can be used if a geometric barrier exists to define the final shape. In the absence of a physical barrier, shape memory can be the answer. Finally, simultaneous shape memory and self-healing would largely extend the possible applications of hydrogels.

The main purpose of this work is to review the recent research on self-healing and shape memory hydrogels, concentrating on the chemical structure of the applied materials and experimental methods. Furthermore, we discuss the molecular mechanisms that lead to the two seemingly different properties. The most important reversible interactions exploited in materials with self-healing and/or shape memory are summarised in Fig. 1 and Table 1. We use this classification as a guide throughout the paper. In the final section,

Table 1
Interactions utilised in self-healing and shape memory hydrogels.

Interaction	Self-healing	Shape memory
Non-covalent interactions		
Hydrophobic association	[33–38][108–110]*	–
Electrostatic interaction	[29,39,41,42]	[93,94][107]*
Metal-ligand coordination	[43–47]	[95,97–99,106]
Hydrogen-bonding	[24,25,48,49][111]*	[100]
Nanocomposite	[26,54–59]	–
Peptide self-assembling	[61–64]	[101,102]
Host-Guest interaction	[27,65,67][112]*	[103][112]*
Crystallisation	–	[15,87–92][108–110]*[111]*
Covalent interactions		
Imine bond	[69]	[106]
Acylhydrazone bond	[70]	–
C-C bond (Diels-Alder reaction)	[71]	–
Phenylboronate ester bond	[72–75][107]*	[105]
Disulphide bond	[70]	[104]

* Hydrogels with both self-healing and shape memory behaviour.