



Feature Article

Reversible disulphide formation in polymer networks: A versatile functional group from synthesis to applications



Benjámín Gyarmati, Árpád Némethy, András Szilágyi*

Soft Matters Team, Department of Physical Chemistry and Materials Science, Budapest University of Technology and Economics, H-1521 Budapest, Hungary

ARTICLE INFO

Article history:

Received 7 August 2012

Received in revised form 27 February 2013

Accepted 4 March 2013

Available online 25 March 2013

Keywords:

Thiolated polymers

Disulphide

Redox sensitivity

Hydrogels

Drug delivery

Self-healing

ABSTRACT

A substantial effort has been made in the last few decades to develop responsive materials that produce a selective answer to well-defined environmental stimuli. In our present review, we focus on the chemistry of thiol–disulphide equilibrium and its incorporation into polymer-based soft materials. Because several papers and extensive reviews have focused on reduction-sensitive drug delivery and gene transfer, we would like to especially emphasise the importance of disulphide formation and the exploitation of reversible thiol–disulphide interconversion in synthesis and its applications. We report the most important synthetic strategies that utilise disulphide formation. However, a major portion of our overview will concentrate on taking advantage of the thiol–disulphide exchange and the reversibility of this reaction in a wide range of applications, such as advanced drug delivery vehicles, bioartificial implants and self-healing and shape-imprinting polymers. In certain cases, the reversibility is only proven and used in one cycle, but in some cases, the process is practically reversible, at least in the time range of the dedicated application. The reversibility of the reaction is an important requirement for the long-term use of these polymers as implant materials; therefore, aside from better understanding the redox processes in living cells, the future direction of this research can lead to the improvement of reversible responses.

© 2013 Elsevier Ltd. All rights reserved.

Contents

1. Introduction	1269
2. Synthesis of thiol–disulphide containing polymer structures	1269
2.1. Incorporation of disulphide bonds directly into polymeric networks	1269
2.2. Synthesis of thiolated polymers	1271
2.3. Characterisation methods for the qualitative and quantitative determination of thiol and disulphide groups	1272
2.4. Effect of reaction conditions on the formation and cleavage of disulphide linkages	1273
3. Application of thiolated polymers and disulphide cross-linked hydrogels	1276
3.1. Injectable polymers with a sol–gel transition	1276
3.2. Targeted drug and gene delivery	1278
3.3. Self-healing materials	1281
3.4. Shape and molecular imprinting	1283
4. Conclusions and outlook	1283
Acknowledgements	1284
References	1284

* Corresponding author. Tel.: +36 14633518.

E-mail address: aszilagyi@mail.bme.hu (A. Szilágyi).

1. Introduction

In recent years, responsive materials, including smart polymer hydrogels, are one of the central aspects of materials science. This can be verified by the increasing number of original research articles and reviews related to their synthesis and possible applications [1–4]. The beauty of this research field is its strong interdisciplinarity; this research requires knowledge of physics, materials science, chemistry, applied biochemistry and cell biology.

Hydrogels are three-dimensional hydrophilic polymer networks that swell but do not dissolve due to the presence of chemical or physical cross-links, and they contain a considerable amount of aqueous fluid. Hydrogels possess several properties that make them biocompatible, such as structural similarities to the body tissues, low friction surfaces and low interfacial tension with the surrounding biological tissues [5,6]. Responsive hydrogels are able to produce a pre-determined response to the alteration of certain environmental stimuli, such as temperature, pH, light (visible or UV), electric or magnetic fields, ionic strength, solvent composition, redox potential or enzymatic conditions, at a desired point and time [7–17]. Due to these attractive physical characteristics and their variable composition, responsive hydrogels are potentially beneficial materials in biotechnology, and they are actively studied. The environmental responsiveness can be exploited in the continuously developing field of targeted drug and gene delivery vehicles, injectable implants, sensors and actuators as well as in modern self-healing materials. We emphasise that utilising pH-sensitivity for targeted drug delivery in the gastrointestinal tract has been well-known for several years and has led to widespread applications of intestine-solvent coatings and delivery vehicles [18], while other types of stimuli (e.g., redox effects) have not yet been exploited in such a wide range in the biomedical field. The main reason for this may be the uncertainty of knowledge on redox gradients in the human body, and the utilisation of redox differences can be more difficult because of the larger variability among patients with the same health state. The key issues of the redox processes in the body and the biological function of glutathione are briefly summarised later in this review. In their work, Meng and co-workers [19] elegantly summarised the advantageous properties of the thiol–disulphide exchange reaction. This exchange reaction is readily reversible without significant heat effects. The disulphide bonds possess excellent stability in circulation and in extracellular physiological conditions, but in a reductive environment, such as cytoplasm, they can undergo rapid cleavage. The time scale of the exchange reaction can be adjusted from minutes to hours.

The first part of this review focuses on incorporating thiol or disulphide functional groups into polymer networks. We report thiol and disulphide groups in our review because of their high biological relevancy, but we must mention that there are several other functional groups that can render redox-responsive properties into a polymer chain (e.g., chelated metal cations [20,21] and ferrocenyl-type groups [22]).

The second part of this review will focus on the applications of the proposed networks. In this field, most of the

publications focus on bioreducible polymers and bioconjugates mainly for biomedical applications [23]. A significantly smaller number of studies are concerned with the utilisation of thiol oxidation and building polymer networks with reversible cross-linking, which is the main focus of the present review. Disulphide bond formation can be utilised in chemical sol–gel synthesis, which allows for an effective and homogenous encapsulation of drugs. This type of entrapment can stabilise the highly ordered structure of proteins and maintain the biological functions of living cells in the polymer matrix. The formation of the polymer matrix by thiol oxidation can be advantageous in the case of injectable implants or simply can be a key step in synthesis strategies. Reversible thiol–disulphide exchange can be triggered to initiate controllable changes in the material properties (e.g., in the modulus of a hydrogel) for several cycles without degradation.

In this review, we discuss the synthetic methods of thiol-modified polymers, which can produce sol-to-gel transitions through the oxidation of thiol groups, followed by recent developments and applications of the thiol–disulphide exchange reaction in diverse areas. This review highlights and emphasises the role of molecular structure in the determination of the macroscopic behaviour of hydrogels.

2. Synthesis of thiol–disulphide containing polymer structures

The chemically reversible cross-linking of natural and synthetic polymer chains has been of considerable interest for decades. The reversible cross-links are usually incorporated into the polymer chains via reductively cleavable disulphide groups. The most frequent reagents to incorporate thiol or disulphide functional groups, as well as the common reducing and oxidising agents in thiol–disulphide chemistry, are listed in Fig. 1.

Two basic synthetic routes are utilised to prepare disulphide cross-linked hydrogels: the application of disulphide-containing molecules to incorporate disulphide groups into the polymer network and the modification of the polymer chains with thiol-containing side chains followed by chemical cross-linking (i.e., the oxidation of thiol groups to establish intermolecular linkages). Both methods have their own applications; each of them is discussed here along with the most relevant characterisation methods for analysing the prepared polymers.

2.1. Incorporation of disulphide bonds directly into polymeric networks

A widely used method for the synthesis of reduction sensitive polymers and hydrogels is the building of disulphide linkages directly between the polymer chains as described in detail in a recent review by Hennink et al. [19]. Two examples are presented here to demonstrate the importance of thiol–disulphide interconversion during the synthesis and application of hydrogels with reversible redox-responses. Disulphide groups can be introduced into a polymeric network simultaneously with the radical polymerisation of the pre-cursor monomers. Ravi et al. [24]

Download English Version:

<https://daneshyari.com/en/article/10609508>

Download Persian Version:

<https://daneshyari.com/article/10609508>

[Daneshyari.com](https://daneshyari.com)