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Thermoresponsive polymers: Insights into decisive hydrogel characteristics, mechanisms of gelation, and promising biomedical applications

Maja Radivojša Matanović, Julijana Kristl, Pegi Ahlin Grabnar *

University of Ljubljana, Faculty of Pharmacy, Aškerčeva 7, Ljubljana 1000, Slovenia

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ABSTRACT

Thermally induced gelling systems have gained enormous attention over the last decade. They consist of hydrophilic homopolymers or block copolymers in water that present a sol at room temperature and form a gel after administration into the body. This article reviews the main types of thermoresponsive polymers, with special focus on decisive hydrogel characteristics, mechanisms of gelation, and biocompatibility. Promising biomedical applications are described with a focus on injectable formulations, which include solubilization of small hydrophobic drugs, controlled release, delivery of labile biopharmaceutics, such as proteins and genes, cell encapsulation, and tissue regeneration. Furthermore, combinations of thermoresponsive hydrogels and various nanocarriers as promising systems for sustained drug delivery are discussed through selected examples from the literature. Finally, there is a brief overview of current progress in nano-sized systems incorporating thermoresponsive properties.

Contents

* Corresponding author. Tel.: +386 147 69621; fax: +386 142 58031.
E-mail address: ahlinp@ffa.uni-lj.si (P.A. Grabnar).

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1. Introduction

Treating a disease with multiple dosing strategies and using conventional drug formulations has many drawbacks. These include fluctuation in drug plasma concentration, various side effects due to the high plasma level of a drug, and ineffective treatment because of the low drug concentration. Another important limitation of multiple dosing regimens is poor patient compliance, especially in diseases that require daily injections for years. Therefore, for effective treatment, it is desirable to maintain drug plasma level within the therapeutic concentration range for as long as the treatment requires. Today researchers are interested in novel drug delivery systems used to direct drugs to the specific site of action and to achieve a controlled release of drug with preferable release kinetics (He et al., 2008). Considering this, there has been growing interest in developing *in situ* forming or gelling systems as appropriate matrices suitable for local and prolonged drug and gene delivery, but also for cell encapsulation and tissue engineering (Janković et al., 2013). These formulations include low-viscous fluids which can be injected into the body prior to gelling or solidifying. In addition, they represent "user-friendly" therapeutics and diagnostics.

A prepared polymer solution can gel after photopolymerization (Burkoth and Anseth, 2000), chemical crosslinking (Ossipov and Hilborn, 2006), or ionic crosslinking (Kuo and Ma, 2001). *In situ* gelling systems that do not require aggressive and complex preparing procedures have gained growing attention. They are called "smart materials" because they respond to change in temperature, pH, or ionic strength (Peppas et al., 2000). Thermally responsive hydrogels have been extensively investigated because of their simple application and low adverse effects on tissues compared to other stimuli (Ruel-Gariépy and Leroux, 2004). Above a certain concentration, they represent a sol at ambient temperature, whereas show gelation in a body (Lai et al., 2014). Their thermoresponsive and biodegradable properties make them potential candidates for drug delivery, cell therapy, as well for tissue engineering.

Thermoresponsive systems for drug delivery are generally classified into hydrogels, interpenetrating networks, micelles, and polymerosomes. Among the most studied are hydrogels, which are insoluble matrices of hydrophilic homopolymers or block copolymer networks that swell in water or physiological fluids (Klouda and Mikos, 2008). Network architecture could be enabled by physical interactions or by chemical crosslinking. Interpenetrating networks are constructed of two chemically linked polymeric conjugates that interact by physical entanglements, providing unique properties to the hydrogel. Micelles are constructed from amphiphilic block copolymers that self-assemble in a solution (Rezaei et al., 2012). Polymerosomes are also formed by self-assembling of block copolymers, but they have a hydrophilic core and a hydrophobic corona. Therefore, they have been used for the delivery of hydrophilic drugs (Ward and Georgiou, 2011).

This article reviews thermoresponsive polymers that form *in situ* gelling systems in aqueous solutions in response to temperature change. The main topics addressed are types and characteristics of polymers, their gelation mechanisms, and promising biomedical uses. Furthermore, the combination of thermoresponsive hydrogels and various nanocarriers, as an advanced system for sustained drug delivery, is discussed through selected examples from the literature. Finally, there is a brief overview of current progress in nanocarrier systems incorporated with thermoresponsive properties.

2. Thermoresponsive polymers

As shown in Table 1, many polymers exhibit a thermoresponsive phase transition property. They can be divided into two major classes based on their origin: naturally occurring polymers and synthetic materials. Cellulose, chitosan, xyloglucan, and gelatin, along with their derivatives, are some examples of natural polymers. Synthetic materials include poly-*N*-isopropylacrylamide (pNiPAAm), poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) (PEO/PPO/PEO) block copolymers, poly(ethylene oxide)-b-poly(D,L-lactic acid-co-glycolic acid)-b-poly(ethylene oxide) (PEO/PLGA/PEO) triblock copolymers, and amphiphilic triblock copolymers, composed of PEO and poly-ε-caprolactone (PCL) (PEO/PCL/PEO). The structures of selected thermoresponsive polymers are presented in Fig. 1. Interest in thermoresponsive polymers has rapidly grown, although the set of polymer structures capable of responding at an application-specific temperature has not grown at the same rate. However, new thermoresponsive polymer compositions are continually being developed with a focus on better biocompatibility and biodegradability. A greater role in the next generation of smart thermosensitive materials is expected (Hennink and van Nostrum, 2012; Roy et al., 2013). Polymers that are able to respond to changes close to body temperature are further discussed in Sections 3 and 4.

Table 1
Thermoresponsive polymers with the decisive hydrogel characteristics.

Thermoresponsive polymers		Gelation mechanism	Gelation concent. (wt%)	Gelation temp. (°C)	Storage modulus at LCST (kPa)	References
Naturally occurring polymers	Gelatine	Coil to triple helix transition	~3	<30[a]	5	(Gillmor et al., 1999)
	MC HPMC	Hydrophobic interactions	1–10	40–50 75–90	~3000 Pa s[b]	(Kim et al., 2012; Sarkar, 1979)
	Chitosan/ polyol salt	Hydrophobic forces	~2	~37	6	(Chenite et al., 2001)
	Xyloglucan	3D-membrane network	1–3	22–27	200	(Nisbet et al., 2006)
Poly(*N*-isopropylacryl amide) (PNiPAAm)	PNiPAAm-co-AA	Hydrophobic interactions, coil to globule transition	0.25–5	30–35	~0.7	(Liu et al., 2004b)
	PNiPAAm-co-PEO		20	~37	2	(Lin and Cheng, 2001)
PEO/PPO/PEO copolymers		Micelle packing and entanglements	≥18	15–30	4–9	(Radivojša et al., 2013; Ricci et al., 2002)
PEO/PLGA/PEO copolymers		Micellar growth, hydrophobic interactons	>16	30–35	0.1–0.3	(Jeong et al., 1999)

[a] Aqueous solution of gelatin gells in response to decrease in temperature (possesses UCST).
[b] The viscosity (η) of MC-based gel.