Biomaterials 35 (2014) 4969–4985

Contents lists available at ScienceDirect

Biomaterials

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

Review

Click hydrogels, microgels and nanogels: Emerging platforms for drug delivery and tissue engineering

Yanjiao Jiang [a], Jing Chen [a], Chao Deng [a,*], Erik J. Suuronen [b], Zhiyuan Zhong [a,*]

[a] Biomedical Polymers Laboratory, and Jiangsu Key Laboratory of Advanced Functional Polymer Design and Application, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, People's Republic of China
[b] Division of Cardiac Surgery, University of Ottawa Heart Institute, Ottawa K1Y 4W7, Canada

ARTICLE INFO

Article history:
Received 24 February 2014
Accepted 3 March 2014
Available online 24 March 2014

Keywords:
Click chemistry
Hydrogels
Microgels
Nanogels
Drug delivery
Tissue engineering

ABSTRACT

Hydrogels, microgels and nanogels have emerged as versatile and viable platforms for sustained protein release, targeted drug delivery, and tissue engineering due to excellent biocompatibility, a microporous structure with tunable porosity and pore size, and dimensions spanning from human organs, cells to viruses. In the past decade, remarkable advances in hydrogels, microgels and nanogels have been achieved with click chemistry. It is a most promising strategy to prepare gels with varying dimensions owing to its high reactivity, superb selectivity, and mild reaction conditions. In particular, the recent development of copper-free click chemistry such as strain-promoted azide-alkyne cycloaddition, radical mediated thiol-ene chemistry, Diels–Alder reaction, tetrazole-alkene photo-click chemistry, and oxime reaction renders it possible to form hydrogels, microgels and nanogels without the use of potentially toxic catalysts or immunogenic enzymes that are commonly required. Notably, unlike other chemical approaches, click chemistry owing to its unique bioorthogonal feature does not interfere with encapsulated bioactives such as living cells, proteins and drugs and furthermore allows versatile preparation of micropatterned biomimetic hydrogels, functional microgels and nanogels. In this review, recent exciting developments in click hydrogels, microgels and nanogels, as well as their biomedical applications such as controlled protein and drug release, tissue engineering, and regenerative medicine are presented and discussed.

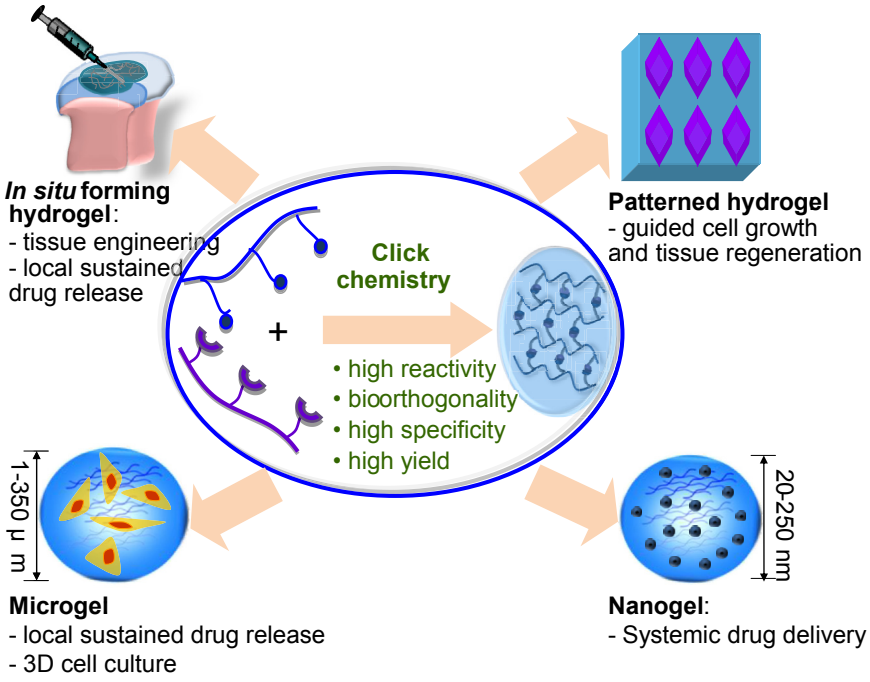
1. Introduction

Hydrogels, microgels and nanogels with excellent biocompatibility, a microporous structure with tunable porosities and pore sizes, and dimensions spanning from human organs, cells to viruses have emerged as a most versatile and viable platform for sustained protein release, targeted drug delivery, and tissue engineering [1–7]. In the past decade, various physical and chemical cross-linking strategies have been developed to fabricate hydrogels, microgels and nanogels [8–10]. The physical hydrogels (e.g. thermosensitive hydrogels, stereocomplexed hydrogels, and ionically crosslinked hydrogels), though formed under particularly mild conditions, are typically weak and exhibit poor long-term stability in tissues [9,11–13]. In contrast, chemical hydrogels, formed from photo-polymerization and enzymatic cross-linking for example, are generally characterized by better stability, durability, and mechanical properties [14,15]. It should be noted, however, that chemical hydrogels often require use of an initiator or enzyme that might introduce potential toxicity concerns. In addition, they may suffer from low specificity, leading to unwanted cross-reactions with drugs, proteins and cells.

In recent years, click chemistry due to its high reactivity, superb selectivity, and mild reaction conditions has appeared as a most promising strategy to prepare hydrogels with varying dimensions and patterns (Scheme 1). The unique bioorthogonality of click reaction renders thus formed hydrogels highly compatible with encapsulated bioactives including living cells, proteins and drugs. For example, hyaluronic acid (HA) hydrogels developed via copper(I)-catalyzed azide-alkene cycloaddition (CuAAC) have been used as drug reservoirs and cell scaffolds [16]. Bisphosphonate-functionalized dextran nanogels crosslinked via CuAAC achieved significant localization in both femur and spine, and provided a possible anti-osteoporotic effect towards bone disease [17]. In

* Corresponding authors. Tel./fax: +86 512 65880098.
E-mail addresses: cdeng@suda.edu.cn (C. Deng), zyzhong@suda.edu.cn (Z. Zhong).

http://dx.doi.org/10.1016/j.biomaterials.2014.03.001
0142-9612/



Scheme 1. Preparation and potential biomedical applications of click hydrogels, microgels and nanogels.

particular, recent development of copper-free click chemistry such as strain-promoted azide-alkyne cycloaddition, radical mediated thiol-ene chemistry, Diels–Alder reaction, tetrazole-alkene photo-click chemistry, and oxime reaction renders it possible to form hydrogels, microgels and nanogels without use of potentially toxic catalysts. Anseth et al. reported that cell-laden hydrogels could be formed from azide functionalized PEG and difluorocyclooctyne (DIFO) functionalized peptide without a copper catalyst [18]. Notably, the biochemical properties of hydrogels could be manipulated with precise spatiotemporal control using photo-initiated thiol-ene reactions to introduce new biomolecules into the hydrogel network.

In this review, exciting developments in click hydrogels, microgels and nanogels, as well as their applications for controlled protein and drug release, tissue engineering, and regenerative medicine are presented and discussed. It is remarkable to note that in less than ten years since the first report, click hydrogels have become a unique and versatile family of biomaterials that provide new opportunities to guide cell phenotypes and function and to control drug and protein release. In particular, recent development of click microgels and nanogels has further offered versatile platforms with varying dimensions for controlled drug release, and (stem) cell culture and management in 3D scaffolds. There are several excellent reviews on the synthesis of biomaterials including polymers, dendrimers and hydrogels via click chemistry [19–24], but none have focused on click hydrogels, microgels and nanogels. Here, we first give an overview on the development of click and pseudo-click strategies for the fabrication of different types of hydrogels (Table 1). Then, preparation and biomedical applications of click microgels and nanogels are presented. Finally, spatiotemporal incorporation of biological cues in hydrogels via click chemistry to construct 3D biomimetic micropatterned scaffolds is discussed.

2. Copper(I)-catalyzed azide-alkyne (CuAAC) click hydrogels

Since the first reports in 2002 by Sharpless and Meldal [25,26], the copper(I)-catalyzed azide-alkyne (CuAAC) click reaction has been viewed as ideal for chemical synthesis, drug discovery, bioconjugation, and biochemistry due to its fast reaction rate, high efficiency, excellent regiospecificity and bioorthogonality [20,27–30]. In particular, alkynes and azides are not present in nature, which renders CuAAC reaction compatible with different drugs, proteins and cells. The reaction kinetics of CuAAC is fast under physiological conditions and typically yields gels within a few seconds to tens of minutes. The first click hydrogels were reported in 2006 by Hilborn et al. from azide and alkyne functionalized poly(vinyl alcohol) (PVA) [31]. The hydrogels were formed with high gel fractions and elastic moduli ranging from 2 to 18.8 kPa using copper sulfate and sodium ascorbate as catalysts. Hawker et al. prepared PEG hydrogels from diacetylene- and tetraazide-functionalized PEG via a CuAAC click reaction [32]. Interestingly, these click hydrogels showed significantly higher tensile strength (up to 2.39 MPa) and strain compared to photochemically cross-linked hydrogels, likely due to the more efficient click reaction. In addition, additives such as carbon black, 4-phosphonooxy-2,2,6,6-tetramethylpiperidyloxy nitroxide and titanium dioxide nanoparticles had little influence on hydrogel formation, supporting that CuAAC click reaction is specific and tolerant of other matters in the reaction mixture. Yang et al. designed and fabricated RGD functionalized PEG hydrogels based on tetraacetylene PEG and diazide-functionalized RGD peptides using $CuSO_4$ and sodium ascorbate as catalysts [33]. The gelation time ranged from 2 to 30 min depending on polymer concentration, temperature and catalyst concentration. The results showed that an increase of RGD peptide concentration from 0.54 to 2.7 mM in hydrogels led to significantly enhanced attachment and proliferation of primary human dermal fibroblasts. Liskamp et al. obtained enzymatically degradable PEG hydrogels from an alkyne-functionalized star-shaped PEG and protease-sensitive diazide-functionalized peptide [34]. These hydrogels were degradable in trypsin and plasmin, and their swelling ratio and storage modulus could be tailored by polymer concentration, molecular weight, and architecture (4- *vs.* 8-arm PEG). Biodegradable hydrogels were also developed from azide-functionalized PEG and alkyne-functionalized poly(trimethylene carbonate) (PTMC) or