Photoresponsive Hydrogels as Drug Delivery Systems

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Hydrogels have been developed and used in tissue engineering and regenerative medicine to deliver therapeutics to injured or diseased tissue because of their versatility and properties that can be tailored to match the natural extracellular matrix. Hydrogels can be made with a variety of physical and chemical properties combined with light responsiveness ideal for applications in different fields of medicine that require the spatiotemporal control of therapeutics. Light, as a stimulus, is relatively inexpensive, contact-free, noninvasive with high spatial resolution and temporal control, convenient and easy to use, and allows deep tissue penetration that is relatively harmless. Photoresponsive hydrogels are ideal candidates for on-demand drug delivery systems that are capable of sustained and controlled drug release, minimizing the side effects, and ensuring the activity and efficient delivery of drugs to the target tissue.

Key words

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INTRODUCTION

Hydrogels are cross-linked polymeric networks based on hydrophilic macromonomers that are able to retain large amounts of water.¹ They are excellent soft materials with tunable chemical structure and physical properties as well as good biocompatibility, biodegradability, limited or minimal toxicity, and simplified synthesis methods.^{2,3} Over the years, hydrogels have evolved from the classical ones to intelligent ones, capable of responding to external stimuli such as pH, light, electricity, magnetic field and enzymes with the proper selection of polymer composition and assembly. This has led to its diverse applications in various fields. In particular, hydrogels have been of great interest in drug delivery, which have been developed in many branches of medicine, including cardiology, oncology, immunology, wound healing, and pain management.⁴⁻⁸

Drug release in response to stimuli or physiologic changes would be an ideal delivery system, wherein drug release is highly controlled and non-specific side effects at the off-target sites are alleviated. These were some critical issues with conventional drug delivery systems that had systemic toxicity and repeated dosing. In contrast to stimuli responsive hydrogels that would serve as drug delivery vehicles with no systemic toxicity and controlled dosing. Stimuli responsive hydrogels ensure that the therapeutic benefits from the drug are optimized. With their tunable physical properties that confer controlled drug release features and ability to protect the drug from degradation, stimuli responsive hydrogels emerge as highly efficient drug delivery systems.

A variety of stimuli responsive hydrogels with delicately controlled physical and chemical properties have been developed in the past decades.^{9,10} Among these are the photoresponsive hydrogels that have gained significant attention largely owing to their amenability to light-induced modulation and their minimal invasiveness for in vivo and clinical applications. Herein we discuss photoresponsive hydrogels and how they could be manipulated and applied for targeted drug delivery applications. Suitable examples from the literature are provided that support the recent advancements of photoresponsive hydrogels in targeted drug delivery in diverse disease areas, and how they could be suitably made to achieve significant impact in targeted drug delivery. Photoresponsive hydrogels with their versatility are promising delivery vehicles of therapeutic molecules in several disease conditions.^{11,12}

LIGHT AS STIMULUS

Interaction of light with photoresponsive hydrogels

Light as stimulus for drug delivery systems is advantageous due to its noninvasive nature, high spatial resolution and temporal control, and convenience and ease of use. For these reasons, light has been extensively applied in a variety of biomedical applications beyond drug delivery, including image-guided surgery, polymerization and degradation of tissue engineering scaffolds, and photodynamic therapy for cancer.^{13,14} In this review, the scope has been limited to light-triggered drug delivery systems that have demonstrated triggered cargo release for each of the major light-responsive drug delivery mechanisms: photochemically triggered release, photoisomerization and photothermal release (Fig. 1). The many mechanisms utilized for light-triggered responses has been previously reviewed.¹⁵⁻¹⁷ Often, photoresponsive hydrogels incorporate photocleavable or photoisomerizable components that allow light-mediated changes in their properties (Table 1). The interaction of light with photoresponsive hydrogels can result in different responses. Depending on the location and type of photoresponsive moiety, light-induced responses could lead to swelling or shrinking, crosslinking or de-crosslinking, degradation or permanent chemical modification, etc. Examples are highlighted herein to illustrate progress for each mechanism, and key limitations are identified to motivate future research and advance the field.

Several works in the field involved the fabrication of photodegradable hydrogels out of different synthetic polymers by incorporating photolabile groups to the polymer backbone. The controlled photodegradation could control the release of therapeutic factor at the target area. In particular, the *o*-nitrobenzyl group (*o*-NB) is frequently utilized and incorporated in polymers. Several works have been done creating a library of polymerizable *o*-nitrobenzyl macromers with varying functionalities to allow for direct conjugation to various bioactive molecules and polymers.¹⁸ Crosslinks containing *o*-nitrobenzyl groups were also used to hold together hydrogels made of polyethylene glycol (PEG) and polyacrylamide (PAM) that when undergoes photodegradation results in release of the model protein. One study incorporated up to three different photocleavable groups into the backbone of PEG macromers to make photodegradable hydrogels.¹⁸ All of the photocleavable groups contained the *o*-NB moiety but they each had varying modifications that changed their reactivity to different wavelengths of light. When exposed to low intensity (< 45 mW/cm²) wavelengths of light rang-

Fig. 1. Mechanisms involved in the light-triggered release of therapeutics in a photoresponsive hydrogel.

Table 1. Lists of some functional groups used in the design of photoresponsive hydrogels that undergo cleavage and isomerization in response to light

Photoreaction & Functional Group	Chemistry (e.g.)	Wavelength	Ref.
Cleavage Nitrobenzyl ester		365 nm	18, 32
Coumarin		>365 nm	33, 34
Isomerization Azobenzene		365 nm, 445 nm	35, 36
Spiropyran		365 nm, Vis	36

Vis, visible light.

ing from 365 to 436 nm for 5 min, the authors demonstrated the triggered sequential release of three different dyes (fluorescein, rhodamine and aminomethylcoumarin acetate). In another study, Liu and their co-workers¹⁹ designed and synthesized a photo and pH dual-sensitive amphiphilic copolymers with photolabile *o*-NB groups that can self-assemble into stimuli-regulated amphiphilic micelles in aqueous solution carrying doxorubicin (DOX) for cancer therapy. The DOX-loaded micelles showed a cumulative release ratio of 10.09 wt% at pH 5.0 after UV-irradiation for 20 min. A high cumulative DOX release ratio (74.70%) at the simulated tumor microenvironment was achieved within 6 days.²⁰ Aside from photodegradable hydrogels, hydrogels with photocontrollable cell adhesion molecules to control biomolecule density and degree of cell attachment to the surface have been prepared utilizing similar photocleavable nitrobenzyl moiety.²¹ Photoreponsive hydrogels have also been investigated and found to be capable of encapsulating and releasing live cells on-demand.²²

These studies have shown the advantages of using light as a stimulus to control the release of therapeutic agents: drugs, proteins and other biomolecules, control cell attachment and growth with adaptive surfaces, and even carry live cells.

Controlled and targeted drug release

Controlled drug release is essential for improving therapeutic efficacy and minimizing adverse effects due to the strong targeted features to regulate the distribution of drugs in vivo. Photoresponsive hydrogels can provide spatial and temporal control in the release of drugs or therapeutics. The 3D networks of hydrogels allow loading of drugs, while its light-induced gel-to-sol transition can be used to release the loaded drug.²³

Recently, NIR-responsive hydrogels (Table 2) have

been of interest as they provide great potentials for therapeutic treatment due to both the low health hazard and deeper light penetration in tissue. In an example, Cao and co-workers developed an NIR-light-controlled drug delivery platform based on the composite hydrogels of low-melting-point agarose and PEGylated black phosphorous (BP) nanosheets.²⁴ In this study, NIR-induced (808 nm) heating due to the photothermal conversion of BP resulting in hydrolysis and subsequent melting of the hydrogel that triggers the controlled release of encapsulated doxorubicin (DOX), a cancer treatment drug. In vivo experiments with tumor tissues also demonstrated this system to be capable of controlling the release of drugs to reduce and eliminate subcutaneous breast and melanoma cancers. The hydrogel is biodegradable and easily excreted through urine after the treatment, which is promising for clinical translation. Further advancement in NIR-responsive hydrogels has led to the development of upconversion nanoparticles, wherein luminescence converts NIR light into UV light. Zhao and co-workers introduced upconversion nanoparticles into PEG hydrogels with photolabile linkers.²⁵ NIR light (980 nm) could then induce the gel-sol transition and trigger the release of biomacromolecules (proteins and enzymes) entrapped in the hydrogel without sacrificing their biocompatibility. These upconversion nanoparticles have been studied and are continually being developed for photodynamic therapy in cancer due to their ability to deliver chemotherapeutic drugs in to the tumor microenvironment.^{26,27} The use of light or laser to control the release and activation of chemotherapeutic drugs on site reducing the toxicity towards healthy surrounding cells or tissue have made such an impact on cancer research.

Laser assisted drug delivery

Lasers have been investigated and used clinically to

Table 2. Other examples of near-infrared (NIR)-responsive hydrogels/ structures that have been developed as delivery systems and the significant findings

Type	Detail	Ref.
Upconversion nanoparticles	Continuous-wave NIR light (980 nm) can be used to induce the sol-gel transition and release large, inactive biomacromolecules (protein and enzyme) entrapped in the hydrogel into aqueous solution "on demand"	25
Injectable supramolecular hydrogel	NIR light-responsive supramolecular hydrogel consisting of α -cyclodextrin and polyethylene glycol CPEG-modified dendrimer-encapsulated platinum nanoparticles release the entrapped therapeutic agents in an on-demand and dose-tunable fashion	37
Composite hydrogel	Dopamine nanoparticle (DP) was incorporated as a highly effective photothermal agent as well as anticancer drug, bortezomib (BTZ) carrier inside a stimuli-responsive pNIPAAm-co-pAAm hydrogel	38
PEG-NH ₂ , ssDNA-caged aptamer nanostructure	NIR light-activated cancer cell targeting and doxorubicin delivery in photothermal therapy	39

enhance the delivery of therapeutic agents that requires deeper penetration. For instance, topical drug delivery, which is essential to dermatological therapy. The cutaneous bioavailability of most topically applied drugs is relatively low with only 1–5% being absorbed into the skin, and some drugs that do get absorbed do not penetrate deeply enough to reach the desired target in the tissue.²⁸ Many medications are too large to penetrate the stratum corneum barrier and require either an injectable or systemic delivery. Laser assisted drug delivery is an evolving modality that could allow for a greater depth of penetration by existing topical medications, and a more efficient method for transcutaneous delivery of large drug molecules.²⁹ One study is the use of laser-assisted delivery to enhance less-permeable drugs and cosmeceuticals in targeting cutaneous lesions for both efficacy and safety.³⁰ Another study investigated the effect of combining laser and application of topical whitening agent together to treat Melasma, a common hyperpigmentation disorder.³¹ These studies have found significantly enhanced penetrations to a certain extent. But the majority of the existing studies on laser assisted drug delivery have been performed on animal models and additional human studies are needed.

CONCLUSIONS AND FUTURE PERSPECTIVES

For the past decades, hydrogels have evolved from the simple chemically or physically cross-linked networks loaded with a single component to the present with complex multicomponent systems capable of releasing multiple therapeutics in a spatially and temporally controlled and triggered manner. The diversity of hydrogel chemical composition and structure combined with a responsiveness to light, a stimulus with various advantages such as being cheap, contact free, and spatiotemporally controllable make photoresponsive hydrogels ideal candidates for applications in a wide range of fields. Although substantial effort has been dedicated to the design and investigation of photoresponsive hydrogels in different fields, most of the present systems are restricted to proof-of-concept studies. Many have demonstrated successes as in vitro, and some have produced promising preclinical in vivo results. However, there have not been any clinical trials for photoresponsive drug delivery systems. This is partly due to the complex design of many systems. Thus, going forward, it will be advantageous to keep the system design simple and straightforward for clinical translation. Nonetheless, we believe that photoresponsive hydrogels will increase their role within the field of therapeutic delivery

with the many exciting approaches currently under way to advance the clinical effectiveness of photoresponsive drug delivery systems.

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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