Controlled Release Targeted Delivery Solubility Enhancement

SHAPE CHANGE POLY(N-ISOPROPYLACRYLAMIDE) MICROSTRUCTURES FOR DRUG DELIVERY



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Introduction

Therapeutic drugs have evolved from single component formulations such as powders to multi-component drug delivery systems (DDSs) such as capsules, anisotropic particles, or microfabricated needle patches. An effective DDS must be both smart and multifunctional; it must release a drug at a specified anatomical location within the therapeutic range for a specified period of time and with minimal side effects. DDSs can target cell receptors using antibodies, ligands, or aptamers for more effective cancer therapeutics[1] or dissolve and release their cargo in specific anatomical areas such as the stomach, which is highly acidic.[2] Thus far, while polymeric DDSs can bind to specific cells or be broken apart by biochemical reactions, they are inherently static and do not reconfigure or change shape dynamically. Shape change is an emerging concept in DDSs which is inspired by robotics and the tunable shapes of cells or pathogens. Shape change offers the possibility for autonomous, environmentally responsive multi-state functionality. There are a number of dynamic polymeric DDSs that range in size from nanometer-sized biomolecular constructs to centimeter-sized implants. These new materials are in different stages of development, ranging from laboratory curiosity to clinical trial. Nanometer-sized dynamic shape change structures for use in DDSs are composed of smart biomolecules, such as DNA, and can be assembled into shapes such as cubical containers with controllable lids.[3] In this article, we restrict our discussion to larger, micro or mesoscale systems and focus on the use of shape change polymer microstructures to create dynamic DDSs based on reversible swelling.

Shape Change Polymer Microstructures

Shape memory polymers and hydrogels are perhaps the most important types of all responsive polymers.[4–6] These systems often are composed of two kinds of molecular moieties, including rigid and flexible chains or hydrophobic and hydrophilic structural units. While the use of shape memory polymers in drug delivery is reviewed elsewhere,[7] we elaborate here on multilayer and patterned microstructures composed of at least one hydrogel component. This paradigm represents an attractive concept for dynamic DDSs for the following reasons:

- Hydrogels have mechanical properties, such as moduli, that are well matched with those of human tissue and organs. Many are biocompatible and capable of swelling by several orders of magnitude in volume in response to a range of different environmental stimuli.[8,9] In aqueous biological systems, swelling or collapse can occur due to absorption or expulsion of water.
- Hydrogel swelling can be achieved in response to various stimuli like pH,[10] temperature,[11] electric field,[12] or biomolecules[13–17] and can be programmed to be responsive to more than one stimulus at a time.[18–20] In addition, gelation can also be triggered *in vivo*.[21]
- Due to large changes in volume, swelling and de-swelling cause large mechanical deformations that can be used to enable actuation without the need for any other external sources of energy such as batteries or wires.
- Multilayers[22] using combinations of more and less swelling hydrogels or gradient crosslinked hydrogels can be designed so that differential volume change during swelling can be converted to spontaneous curving and folding to form a wide range of three-dimensional (3D) shapes and structures.[23–25]
- With advances in bio-MEMS, a number of techniques have been developed to pattern and structure hydrogels in a wide range of shapes and sizes using mass-producible methods such as photolithography, printing, molding, or layer by layer assembly methods.