Controlled Release | Targeted Delivery | Solubility Enhancement

POLY(N-ISOPROPYLACRYLAMIDE)-BASED STIMULI-RESPONSIVE MATERIALS


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Introduction

Controlled delivery of therapeutic agents has generated significant interest[1–3] because it can improve drug efficacy by preventing premature degradation, enhance uptake, reduce side effects, and help to maintain appropriate therapeutic concentration in the bloodstream. Significant research effort has been devoted to the development of systems that can deliver defined quantities of a therapeutic payload in a site-specific and/or time-controlled fashion. Devices made with stimuli-responsive materials have attracted considerable interest for use in controlled delivery.[4–6] Stimuli-responsive or "smart" materials undergo dramatic property changes in response to small changes in the environment and can be used as programmable, responsive, and adaptive materials. The response may be produced through artificial stimuli such as thermal, light-irradiation, magnetic, ultrasonic, and electric, as well as natural stimuli like changes in pH, ionic strength, redox gradients, and enzymatic stimuli.[4] The use of stimuli-responsive delivery devices offers an interesting opportunity for controlled delivery where the delivery system becomes an active participant rather than a passive vehicle in the optimization of a therapy.[7] The benefit of stimuli responsive nano-carriers is especially important when the stimuli are unique to disease pathology, allowing the nano-carrier to respond specifically to the pathological "triggers" such as pH, temperature, and redox microenvironment.

Poly(N-isopropylacrylamide): A Temperature-sensitive Polymer

Among the stimuli-responsive materials, thermo- and pH-sensitive materials are the most frequently used for controlled drug delivery because of the different thermal and pH conditions within various tissue and cellular compartments along the endocytic pathway.[8,9] For example, tumor tissues have slightly higher temperature and lower pH than healthy tissues. These variations in temperature and pH can be exploited for the targeted release of payloads at specific sites.[9] Stimuli-responsive drug delivery platforms often are prepared by formulating or functionalizing the system with thermo- and/or pH-sensitive polymeric materials.[10] These materials have polymer–polymer and polymer–solvent interactions that change abruptly with a small change in pH and/or temperature, which translates to a polymer chain transition between extended and compacted coil states. In drug delivery, this chain configuration disrupts the integrity of the delivery vehicle and triggers release of the drug.

Poly(N-isopropylacrylamide) (PNIPAM) (**Figure 1**) is a unique hydrophilic polymer with a stimuli-responsive transition temperature close to physiological temperature.

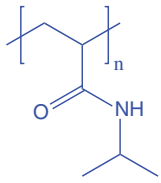

Figure 1. Structure of PNIPAM.

In aqueous solution, PNIPAM exhibits a thermo-responsive phase transition at 32 °C. This transition temperature is called the lower critical solution temperature (LCST). Below the LCST, PNIPAM is water-soluble and hydrophilic, with an extended chain conformation. At LCST, PNIPAM undergoes a phase transition to a hydrophobic aggregate state becoming water insoluble above the LCST. This phase transition occurs within a remarkably narrow temperature range and is reversible. The macroscopic manifestation of this thermal change depends on the chain configuration (**Figure 2**).[11]

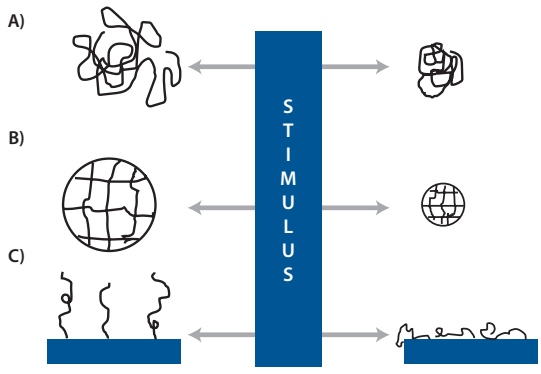

Figure 2. Classification of stimuli-responsive polymers by their physical form and their response to external stimuli. **A**) Linear free chains in solution will undergo a reversible collapse after stimulus is applied. **B**) Covalently crosslinked reversible gels where swelling or shrinking of the gels can be triggered by environmental change. **C**) Chain adsorbed or surface-grafted form, where the polymer reversibly swells or collapses on the surface once an external parameter is changed.[11]