Application of Poly(N-isopropylacrylamide) As Thermosensitive Smart Materials

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Abstract. Drug delivery systems refer to a technical system capable of comprehensively regulating the distribution of drugs in a living body in terms of time, space and dose. As thermosensitive smart materials, Poly(N-isopropylacrylamide) (PNIPAM) is an ideal treatment platform for the development of drug delivery systems. This article focuses on the application of various thermally sensitive smart materials such as nanoparticles, nanofibers, hydrogels, and self-assembled micelles in drug delivery systems prepared by PNIPAM in recent years. The future development of PNIPAM thermosensitive smart materials is also discussed.

1. Introduction
As the fourth generation of materials, following natural materials, synthetic polymer materials and artificial design materials, smart materials are a new type of functional materials that can respond to stimuli in their environment[1], such as temperature[2], pH[3], light[4] stimuli and so on. This behavior enables them to play an important role in biological, medical and environmental fields. Among them, thermosensitive smart materials, which are sensitive to temperature, have been studied intensively over many years. The applications of thermosensitive smart materials show a great deal of variety in biomedical, from drug delivery[5-6] to tissue engineering [7-8](Fig. 1).

Fig. 1 Application of thermosensitive smart materials in biomedical.
Among a variety of thermosensitive smart materials, poly(N-isopropylacrylamide) (PNIPAM) first reported in 1968[9], is one of the most widely investigated polymer[10]. PNIPAM has both hydrophilic amido groups and hydrophobic isopropyl groups. When the temperature is low, there is a strong hydrogen bond between the amide groups and the external water molecules. PNIPAM is hydrophilic, macroscopically swelling occurs for the volume. When the temperature reaches the low critical dissolution temperature(LCST), the hydrogen bond between the amide group and the water molecule is destroyed, the hydrophobicity of the isopropyl group in the structure plays a leading role, and PNIPAM becomes hydrophobic and gradually shrinks (Fig. 2). Many studies have shown that the LCST of PNIPAM is about 32°C[11], which is close to physiological temperature and easy to adjust, so it has been developed for biomedical, e.g., drug delivery systems[12], cardiovascular repair[13], sensing analysis[14], medical imaging [15] and so on. In this review, we focus mainly on the application of PNIPAM as thermosensitive smart materials in drug delivery systems.

Fig. 2 Chemical structure (a) and temperature respond (b) of PNIPAM[16].

2. Application of PNIPAM in drug delivery systems

Drug delivery systems refer to a technical system capable of comprehensively regulating the distribution of drugs in a living body in terms of time, space and dose. The goal is to deliver the right amount of drug to the right place at the right time, thereby increasing the bioavailability of the drug, improving efficacy and reducing costs while reducing toxic side effects. However, due to the great changes in the physiological conditions between the normal microenvironment and the diseased parts of the human body, the ordinary drug delivery systems may not be able to achieve the desired goal in the complex pathological microenvironment. Therefore, there is a great need for smart materials, especially PNIPAM with temperature stimulus response functions, in drug delivery systems[17]. Various thermosensitive smart materials made by PNIPAM include nanoparticles[18], nanofibers[19], hydrogels[20], self-assembled micelles[21] etc.

Lu[22] prepared PNIPAM-DOX-CPNs (conjugated polymer nanoparticles) by nanoprecipitation based on poly (fluorene-ethylene), PNIPAM and antitumor model drugs doxorubicin (DOX) (Fig. 3). In Vitro drug release experiments demonstrated, at pH 5.5 and 37°C, more than 70% of DOX was released and when the mass concentration ratio of PFV/PNIPAM is 4:1, under the same conditions, the drug release effect of nanoparticles was better than other ratios of nanoparticles. Furthermore, this research indicated that PNIPAM-DOX-CPNs provide a new method for controlling and tracking drug delivery and effective chemo-/photodynamic therapy synergistic therapy. In recent decades, multimodal combination therapies have caused great clinical attention. Geng[23] fabricated DOX-loaded D-PPy@PNAs nanogels as drug delivery platform(Fig. 4), which also combined near-infrared photothermal therapy (NIR-PTT) with chemotherapy to maximize the synergistic effect of thermo-induced chemotherapy sensitization and improve the treatment effect.
Hyperthermia for cancer treatment requires human tissue to be exposed to temperatures above normal body temperature (up to 45 °C)[24], but the LCST of PNIPAM is about 32°C. Therefore, it cannot meet the needs of hyperthermia. Wei[25] prepared curcumin-loaded PNIPAM-N-methylolacrylamide-acrylamide (PNIPAM-NMA-Am) nanofibres by way of radical copolymerization and electrospinning technology. In this report, with the introduction of the hydrophilic group Am, the LCST of PNIPAM increased from 32°C to 63°C. The total immersion experiment showed that the release of curcumin from nanofibers gradually increased with time, at 60°C, 80% curcumin was released. Meanwhile cytotoxicity test indicated that the PNIPAM-NMA-Am nanofibres is non-toxic. Therefore, PNIPAM-NMA-Am nanofibres has the potential to be applied in drug delivery systems. In addition, macro-nanofibers with extremely large surface area and porosity are also preferred candidates for drug carriers[26-27]. Based on poly(N-isopropylacrylamide-co-acrylic acid) and regenerated silk fibroin (a protein polymer with good biocompatibility and biodegradation), Li[28] designed rhodamine B-loaded P(NIPAAM-co-AAc)/RSF fibrous mats and the drug release behavior of the fibrous mats at different temperatures and pH was studied (Fig. 5). The results showed that rhodamine B-loaded P(NIPAAM-co-AAc)/RSF fibrous mats display temperature and pH dual responsive controlled release behavior. When the temperature increased from 25°C to 60°C, the cumulative release of rhodamine B increased from 56% to 74% within 110 h (Fig. 5a). At the same time, when the pH value increased from 5.7 to 6.6, the release of rhodamine B decreased from 68% to 53% (Fig. 5b). For the controlled release diagram of rhodamine B, please refer to Fig. 5c.
Fig. 5 The release profiles of rhodamine B-loaded P(NIPAAM-co-AAc)/RSF fibrous mats with a pH of 5.7 at different temperature (a) and with different pH at 40°C (b) and schematic diagram at different temperature and pH (c)[28].

Since Tanaka[29] first discovered in 1984 that PNIPAM hydrogels also have temperature-induced volume phase transition behavior, PNIPAM thermosensitive smart hydrogels have been widely used in drug delivery systems[30]. However, for PNIPAM, most researchers study the polymerization of their monomers with other substances to maintain their thermal responsiveness[31], ignoring that they do not have sol-gel reversibility, which prevents its application in medical injection systems. Cao[32] developed reversible thermo-responsive I3K peptide−PNIPAM hydrogels with LCST of 33°C, showing a significant reversible sol-gel transition. Then G(IKK)3I-NH2 was loaded into the hydrogels by solution mixing. Through drug release experiments, it was found that above the LCST, G(IKK)3I-NH2 could be released in a continuous linear manner. Therefore, the system can be used as an injectable hydrogel for drug delivery. Renewable biomacromolecules, such as polysaccharides, have been widely developed to design smart hydrogels for drug delivery due to their good biocompatibility, low cost, and environmental friendliness[33]. Recently, based on tremella polysaccharide (WSK), carboxymethyl cellulose (CMC) and glycoside surfactant decyl polysaccharide (C10APG), Zhao[34] fabricated indomethacin (IND)-load WSK/CMC/PNIPAM/C10APG hydrogels with pH and thermosensitive.

Compared with other nanocarriers, copolymer micelles prolong the blood circulation time of the drug and enhance the drug's efficacy, due to the hydrophilic segments of the shell form hydrophilic clouds on the surface of the micelles to avoid the chance of the drug being taken up by the reticuloendothelial system[35]. Luo[36] designed the four-armed star camptothecin(CPT)-loaded (PNIPAM)m-b-hydroxyl-terminated polybutadiene-b-(PNIPAM)m thermosensitive block copolymers micelles, with LCST about 33-35°C, by atom transfer radical polymerization and dialysis. Drug release in vitro showed, at pH 7.4 and 37°C, about 91% of CPT was released within 48 h. The reason may be that the polymer's unique four-arm star structure provides better stability for copolymer micelles. In this research the thermosensitive block copolymers micelles produce relatively slow and more controlled release of the wrapped CPT during the entire release process, which is important for drug delivery. Tang[37] developed DOX-loaded poly(propylene sulfide)-b-PNIPAM copolymer micelles, which were dual response to temperature and reactive oxygen species (ROS), with LCST about 35.9-37.1°C. At 37°C and 0.1% H2O2, the drug release of copolymer micelles was 51% at 10h, which is beneficial for drug delivery of inflammatory cancer cells. Furthermore, multicompartment worm-like micelles (MCMs)[38] with unique structural geometry and the potential to deliver two or more incompatible agents[39] have attracted more attention in drug delivery systems[40]. Yue[41] fabricated pupa-like MCMs on the basis of the polystyrene-block-poly(4-vinylpyridine) (PS-b-P4VP) and polystyrene-block-poly(N-isopropylacrylamide) (PS-b-PNIPAM) block copolymer [Fig. 6]. This study might provides new ideas for the application of PNIPAM in biomedicine.
3. Conclusions and Perspectives

This article focuses on the application of various thermally sensitive smart materials such as nanoparticles, nanofibers, hydrogels, and self-assembled micelles in drug delivery systems prepared by PNIPAM in recent years. Even though PNIPAAm has been studied for decades, in addition to the temperature-responsive polymer PNIPAAm, more and better additional co-functionality needs to be introduced to create unique and versatile temperature-responsive polymers[42]. In addition, despite PNIPAM is widely used as thermosensitive smart materials for drug delivery, there have been no reports of any attempts or clinical trials to transform thermal-responsive nanocarriers of polymers into clinics[43].

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